



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/47, 16/18, G01N 33/53	A1	(11) International Publication Number: WO 98/53061 (43) International Publication Date: 26 November 1998 (26.11.98)																		
(21) International Application Number: PCT/AU98/00380 (22) International Filing Date: 22 May 1998 (22.05.98) (30) Priority Data: <table border="0"> <tr> <td>PO 6972</td> <td>23 May 1997 (23.05.97)</td> <td>AU</td> </tr> <tr> <td>PO 6973</td> <td>23 May 1997 (23.05.97)</td> <td>AU</td> </tr> <tr> <td>PO 6974</td> <td>23 May 1997 (23.05.97)</td> <td>AU</td> </tr> <tr> <td>PP 1458</td> <td>22 January 1998 (22.01.98)</td> <td>AU</td> </tr> <tr> <td>PP 1459</td> <td>22 January 1998 (22.01.98)</td> <td>AU</td> </tr> <tr> <td>PP 1460</td> <td>22 January 1998 (22.01.98)</td> <td>AU</td> </tr> </table> (71) Applicant (for all designated States except US): THE COUNCIL OF THE QUEENSLAND INSTITUTE OF MEDICAL RESEARCH [AU/AU]; 300 Herston Road, Brisbane, QLD 4029 (AU). (72) Inventors; and (75) Inventors/Applicants (for US only): HAYWARD, Nicholas [AU/AU]; 13 Prince Street, Paddington, QLD 4064 (AU). SILINS, Ginters [AU/AU]; 35 Eppalong Street, The Gap, QLD 4061 (AU). GRIMMOND, Sean [AU/GB]; Medical Research Council, Harwell, Didcot, Oxfordshire OX11 0RD (GB). GARTSIDE, Michael [AU/AU]; 19 Thomas Street, Camp Hill, QLD 4152 (AU). HANCOCK, John [AU/AU]; 141 Airley Road, Pullenvale, QLD 4069 (AU).		PO 6972	23 May 1997 (23.05.97)	AU	PO 6973	23 May 1997 (23.05.97)	AU	PO 6974	23 May 1997 (23.05.97)	AU	PP 1458	22 January 1998 (22.01.98)	AU	PP 1459	22 January 1998 (22.01.98)	AU	PP 1460	22 January 1998 (22.01.98)	AU	(74) Agents: HUGHES, E., John, L. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
PO 6972	23 May 1997 (23.05.97)	AU																		
PO 6973	23 May 1997 (23.05.97)	AU																		
PO 6974	23 May 1997 (23.05.97)	AU																		
PP 1458	22 January 1998 (22.01.98)	AU																		
PP 1459	22 January 1998 (22.01.98)	AU																		
PP 1460	22 January 1998 (22.01.98)	AU																		
(54) Title: THREE NOVEL GENES ENCODING A ZINC FINGER PROTEIN, A GUANINE, NUCLEOTIDE EXCHANGE FACTOR AND A HEAT SHOCK PROTEIN OR HEAT SHOCK BINDING PROTEIN (57) Abstract <p>The present invention relates generally to three novel human genes with gene regulatory function. These genes encode a zinc finger protein, a guanine nucleotide exchange protein and a heat shock protein or heat shock binding protein. The invention includes derivatives and mammalian animal, insect, nematodes, avian and microbial homologues of these genes. The present invention further provides pharmaceutical compositions and diagnostic agents as well as genetic molecules useful in gene replacement therapy and recombinant molecules useful in protein replacement therapy.</p>																				

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

THREE NOVEL GENES ENCODING A ZINC FINGER PROTEIN, A GUANINE, NUCLEOTIDE EXCHANGE FACTOR AND A HEAT SHOCK PROTEIN OR HEAT SHOCK BINDING PROTEIN

FIELD OF THE INVENTION

5 The present invention relates generally to a novel human gene and its derivatives and to mammalian, animal, insect, nematodes, avian and microbial homologues thereof. The present invention further provides pharmaceutical compositions and diagnostic agents as well as genetic molecules useful in gene replacement therapy and recombinant molecules useful in protein replacement therapy.

10

BACKGROUND OF THE INVENTION

Bibliographic details of the publications referred to by author in this specification are collected at the end of the description.

15

The increasing sophistication of recombinant DNA technology is greatly facilitating research and development in the medical and allied health fields. There is growing need to develop recombinant and genetic molecules for use in diagnosis and in conventional pharmaceutical preparations as well as in gene and protein replacement therapies.

20

In work leading up to the present invention, the inventors sought to identify and clone human genes which might be useful as potential diagnostic and/or therapeutic agents. Molecules of particular interest targeted by the inventors were gene regulators including regulatory proteins, signal transducers and heat shock proteins.

25

Gene expression generally requires interaction between a regulatory protein and an appropriate recognition sequence of a target gene. Regulatory proteins comprise in many cases a domain or motif which facilitates binding to DNA. One particular motif comprises small sequence units repeated in tandem with each unit folded about a zinc atom to form separate structural domains.

30 This motif is now referred to as a zinc finger domain. Such a domain is generally defined by the number of cysteine (C) and histidine (H) residues.

- 2 -

In addition, knowledge of cellular interaction in the control of cell proliferation is essential in the rational design of specific therapeutic strategies aimed at controlling proliferative disorders. Such proliferative disorders including a range of cancers, inflammatory conditions and atherosclerosis. An important aspect of cellular interaction is in signal transduction *via* receptors
5 to intracellular transducers. One key signal transducer is Ras which couples the receptors for diverse extracellular signals to different effectors. Ras directly activates the downstream kinase Raf which in turn induces the mitogen activated protein kinase (MAPK) cascade.

Another regulatory mechanism involves heat shock proteins. The *Escherichia coli* heat shock
10 protein, DnaJ, is the founding member of a family of proteins which are associated with protein folding, protein complex assembly and transit through subcellular components.

Prokaryotic and eukaryotic DnaJ homologues have a modular organisation consisting of a J domain, a glycine-rich spacer, CXXCXGXG [SEQ ID NO:1] repeats and a C-terminal region
15 with no obvious sequence features, as well as additional sequences for protein targeting. The J domain is anticipated to mediate interaction with heat shock 70 proteins (Hsp70) and consists of some 70 amino acids, frequently located at the N-terminus of the protein.

In accordance with the present invention, a genes have been identified from the human genome
20 which encodes proteins having a regulatory role. One gene, in accordance with the present invention encodes a protein with an N-terminal region resembling a zinc-finger domain of a novel type. Another gene encodes a protein involved in guanine nucleotide exchange factor (GEF) signalling pathways. Yet another gene encodes a protein which is a heat shock protein or heat shock-like protein which may have a role in tumour suppression.

25

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a
30 stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Sequence identity numbers (SEQ ID NOs.) for nucleotide and amino acid sequences referred to in the subject specification are defined after the bibliography. A summary of SEQ ID NOs. is also given in Table 1.

- 5 One aspect of the present invention contemplates an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an amino acid sequence having homology to a regulator of gene expression or a derivative of said gene regulator.
- 10 Another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a regulator of gene expression wherein said regulator comprises a zinc finger domain of an $(\text{HC}_3)_2$ type.

Yet another aspect of the present invention is directed to an isolated nucleic acid molecule
15 comprising a sequence of nucleotides or a complementary form thereof selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:2;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:3;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence
20 of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions at 42°C to the nucleotide sequence set forth in (i), (ii) or (iii).

The nucleotide sequence set forth in SEQ ID NO:2 defines the gene, *mcg4*. This gene encodes
25 a product, MCG4, having an amino acid sequence set forth in SEQ ID NO:3.

Even yet another aspect of the present invention provides a genetic construct comprising a vector portion and an animal, more particularly a mammalian and even more particularly a human *mcg4* gene portion, which *mcg4* gene portion is capable of encoding an MCG4 polypeptide or a
30 functional or immunologically interactive derivative thereof.

- 4 -

Still yet another aspect of the present invention contemplates a method of detecting a condition caused or facilitated by an aberration in *mcg4*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg4* wherein the presence of such a nucleotide substitution, deletion
5 and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

Even still a further aspect of the present invention relates to a method of detecting a condition caused or facilitated by an aberration in *mcg4*, said method comprising screening for a single or
10 multiple amino acid substitution, deletion and/or addition to MCG4 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

Another aspect of the present invention contemplates a method for detecting MCG4 or a derivative thereof in a biological sample said method comprising contacting said biological
15 sample with an antibody specific for MCG4 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG4 complex to form, and then detecting said complex.

A further aspect of the present invention contemplates an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an
20 amino acid sequence having homology to a guanine nucleotide exchange factor (GEF) or a derivative thereof.

Yet another aspect of the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides or a complementary form thereof selected from:

25

- (i) a nucleotide sequence set forth in SEQ ID NO:4 or 6;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:5 or 7;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence
30 of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions to the

- 5 -

nucleotide sequence set forth in (i), (ii) or (iii).

The nucleotide sequence set forth in SEQ ID NO:4 or 6 defines the gene, *mcg7*. This gene encodes a product, MCG7, having an amino acid sequence set forth in SEQ ID NO:5 or 7.

5

Even yet another aspect of the present invention provides a genetic construct comprising a vector portion and an animal, more particularly a mammalian and even more particularly a human *mcg7* gene portion, which *mcg7* gene portion is capable of encoding an MCG7 polypeptide or a functional or immunologically interactive derivative thereof.

10

Still yet another aspect of the present invention contemplates a method of detecting a condition caused or facilitated by an aberration in *mcg7*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg7* wherein the presence of such a nucleotide substitution, deletion
15 and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

Even still a further aspect of the present invention relates to a method of detecting a condition caused or facilitated by an aberration in *mcg7*, said method comprising screening for a single or
20 multiple amino acid substitution, deletion and/or addition to MCG7 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

Another aspect of the present invention contemplates a method for detecting MCG7 or a derivative thereof in a biological sample said method comprising contacting said biological
25 sample with an antibody specific for MCG7 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG7 complex to form, and then detecting said complex.

Yet another aspect of the present invention contemplates an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an
30 amino acid sequence having homology to a heat shock protein or a heat shock binding protein or a derivative thereof.

Another aspect of the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides or a complementary form thereof selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:8;
- 5 (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:9;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions at 41°C to the nucleotide sequence set forth in (i), (ii) or (iii).

10

The nucleotide sequence set forth in SEQ ID NO:8 defines the gene, *mcg18*. This gene encodes a product, MCG18, having an amino acid sequence set forth in SEQ ID NO:7.

Even yet another aspect of the present invention provides a genetic construct comprising a vector
15 portion and an animal, more particularly a mammalian and even more particularly a human *mcg18* gene portion, which *mcg18* gene portion is capable of encoding an MCG18 polypeptide or a functional or immunologically interactive derivative thereof.

Still yet another aspect of the present invention contemplates a method of detecting a condition
20 caused or facilitated by an aberration in *mcg18*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg18* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

25

Even still a further aspect of the present invention relates to a method of detecting a condition caused or facilitated by an aberration in *mcg18*, said method comprising screening for a single or multiple amino acid substitution, deletion and/or addition to MCG18 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

30

Another aspect of the present invention contemplates a method for detecting MCG18 or a

- 7 -

derivative thereof in a biological sample said method comprising contacting said biological sample with an antibody specific for MCG18 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG18 complex to form, and then detecting said complex.

5

A summary of SEQ ID Nos. referred to in the subject specification is shown in Table 1.

TABLE 1
SUMMARY OF SEQ ID Nos.

5	SEQ ID NO.	DESCRIPTION
	1	amino acid repeat sequence in DnaJ homologues
	2	Nucleotide sequence of <i>mcg4</i>
	3	amino acid sequence of MCG4
	4	nucleotide sequence of <i>mcg7</i>
10	5	amino acid sequence of MCG7
	6	nucleotide sequence of <i>mcg7</i> within exon of nucleotides 183-288
	7	amino acid sequence of MCG7 within exon of nucleotide 183-288
	8	nucleotide sequence of <i>mcg18</i>
	9	amino acid sequence of MCG18
15	10-18	amino acid sequence identified using BESTFIT
	19	sequence of pGEX and <i>mcg7</i> junction
	20	sequence of pGEX and <i>mcg7</i> junction
	21	nucleotide sequence of <i>myc</i> -tag/ <i>mcg7</i> junction
	22	amino acid sequence corresponding to SEQ ID NO:21
20	23	nucleotide sequence of pGEX and <i>mcg7</i> junction
	24	amino acid sequence corresponding to SEQ ID NO:23
	25-36	<i>mcg7</i> -specific oligonucleotide
	37-45	<i>mcg18</i> -specific oligonucleotide

25 Single and three letter abbreviations for amino acid residues are shown in Table 2.

- 9 -

TABLE 2

Amino Acid	Three-letter Abbreviation	One-letter Symbol
5		
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
10 Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
15 Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
20 Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
25 Valine	Val	V
Any residue	Xaa	X

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a representation of the nucleotide sequence [SEQ ID NO:2] and corresponding amino acid sequence [SEQ ID NO:3] of *mcg4*.

5

Figure 2 is a representation of the alignment of the human MCG4 amino acid sequence with a translation of a partial murine expressed sequence tag (EST).

Figure 3 is a representation of the alignment of the human MCG4 amino acid sequence with a
10 translation of a partial nematode EST.

Figure 4 is a diagrammatic representation showing a predicted structure of MCG4 where H and C represent histidine and cysteine residues, respectively and X refers to any amino acid residue. Zn represent zinc atoms.

15

Figure 5 is a representation of sensitive sequence homology search of related cysteine-containing motifs in another *Caenorhabditis elegans* protein.

Figure 6 is a representation showing that a related cysteine containing motif is present in the
20 GATA-binding transcription factor from *Saccharomyces pombe*.

Figure 7 is a Northern blot showing expression of *mcg4* in various cultured human cancer cell lines. Lanes 1-5, respectively, represent the hybridization signal from 15µg total RNA derived from various human cancer cell lines. Lanes 1-5, respectively, contain RNA from H69 lung
25 carcinoma cells, JAM ovary carcinoma cells, BT20 breast carcinoma cells, HaCat transformed keratinocytes, T24 bladder carcinoma cells.

Figure 8 is a representation of a partial alignment of *mcg4* with human ESTs AA074703 and AA134788.

30

Figure 9 is a representation of the partial nucleotide sequence alignment between a human

(W32939) and mouse (AA242159) *mcg4*-like EST in the putative 5' UTR of the *mcg4* cDNA. The putative initiation codon is underlined and the region upstream represents 5' UTR.

Figure 10 is a representation showing MacVector alignment of MCG4 with forward translations of ESTs AA134788 and AA074703. The nucleotide sequences are shown in Figure 8.

Figure 11 is a diagrammatic representation of the domains of MCG4

zinc finger consensus: CX₂HX₄CX₂CX₄HX₂CX₁₇CX₂CX₁₈HX₂CX₁₈CX₂C

acidic domain consensus: 9/34 amino acids negatively charged, 0/34 positively charged

10 basic domain consensus: 13/55 amino acids positively charged, 0/55 negatively charged

leucine zipper domain consensus: LX₆LX₆RX₆LX₆L

alternate "novel" leucine zipper-like motif where leucine would not be aligned along the one surface of an alpha helix domain: (aa261) LX₆LXLX₆LXLX₆L (aa 286).

15 **Figure 12** is a representation showing similarity of MCG7 with GEFs of various organisms.

Figure 13(a) is a representation of the nucleotide sequence [SEQ ID NO:4] and corresponding amino acid sequence [SEQ ID NO:5] of *mcg7*. Nucleotides 183-288 are an alternative spliced exon (shown in lower case).

20

Figure 13(b) is a representation of the partial nucleotide sequence [SEQ ID NO:6] and corresponding amino acid sequence [SEQ ID NO:7] of *mcg7* but without the exon shown in Fig. 13(a). Amino acids have been numbered from the first methionine codon (underlined). The cDNA molecules of Fig. 13(a) and Fig. 13(b) differ by the inclusion and exclusion of the exon
25 of nucleotides 183-288.

Figure 14 is a representation showing a comparison between MCG7 and a homologue from *Caenorhabditis elegans* using the BESTFIT algorithm. In the figure, the following sequences are underlined:

30

EF-Hand= PROSITE DATABASE NO. PD0C00018

- 12 -

1a nematode DVDEEDEVEDIEF [SEQ ID NO:10]
 1b human DVDGDGHISQEEF [SEQ ID NO:11]
 nematode DHDRDGFISQEEF [SEQ ID NO:12]
 1c human DQNQDGCISREEM [SEQ ID NO:13]
 5 nematode DVDMDGQISKDEL [SEQ ID NO:14]

GUANINE NT BINDING REGION = BLOCKS DATABASE NO. BL00720B

2 human HFVHVAEKLLQLQNFTLMAVVGGLSHSSISRLKETH[SEQ ID NO:15]
 nematode KFVHVAKHLRKINNFTLMSVVG GITHSSVARLAKTY
 10 [SEQ ID NO:16]

DaG-PE BINDING DOMAIN = PROSITE DATABASE NO. PD0C00379

3 human HNFQESNSLRPVACRHCKALILGIYKQGLKCRACGVNCHKQCKDRLSVEC
 [SEQ ID NO:17]
 15 nematode HNFHETTFLTPTCNHCKNLLWGILRQGFCKDCGLAVHSCCKSNAVAEC
 [SEQ ID NO:18]

Figure 15 is a representation of an alignment of human and a partial (5' UTR and partial coding sequence) murine *mcg7* cDNA (GenBank Acc. No. W71787 and AA237373). The putative
 20 initiation codon is underlined. The murine sequence represents a composite of 2 partial cDNA sequences from the EST database (accession numbers W71787 and AA237373). Nucleotide differences between human and murine sequences are shown in lower case lettering and identical residues are indicated with asterisks.

25 **Figure 16** is a representation of further 5' nucleotide and corresponding amino acid sequence for human *mcg7*. Nucleotide positions 1-321 were derived from GenBank Acc. No. AC000134 and nucleotides 322 onwards from Fig. 13(a). Two in-frame initiation codons are underlined. Asterisks denote in-frame stop codons.

30 **Figure 17** is a graphical representation of a GDP release assay. □ Experiment #1 (mean of duplicates). ◇ Experiment #2 (mean of duplicates). The exchange reaction contained 36pmols

of GST-MCG (N-terminally truncated; encoded by Construct B in Fig. 18) and 1.6-12.8 pmols of recombinant GST-N-Ras.GDP. Reaction time 6 mins.

Estimated reaction constants:

$K_m = 2.1 \mu\text{M}$, $V_{max} = 37 \text{pMol}/6 \text{min}/36 \text{pMol}$ [Expt#1]

5 $K_m = 1.5 \mu\text{M}$, $V_{max} = 30.3 \text{pMol}/6 \text{min}/36 \text{pMol}$ [Expt#2]

Figure 18 depicts various recombinant plasmids containing partial or full-length *mcg7*.

Figure 19 is a representation of the nucleotide sequence [SEQ ID NO:8] and corresponding
10 amino acid sequence [SEQ ID NO:9] of *mcg18*.

Figure 20 is a representation showing that MCG18 has partial homology to *E. coli* DnaJ.

Figure 21 is a representation showing that MCG18 has homology to two *Caenorhabditis elegans*
15 proteins.

Figure 22 is a representation showing that MCG18 has homology to a *Saccharomyces pombe* protein.

20 **Figure 23** is a representation showing homology of MCG18 to a *Drosophila virilis* protein.

Figure 24 is a representation showing homology of MCG18 to human DnaJ proteins HDJ-2/HSDJ, HDJ-1/HSP40 and HSJ1.

25 **Figure 25** is a representation of the nucleotide and corresponding amino acid sequence of murine *mcg18*.

Figure 26 is a representation of homology between human and murine MCG18.

30 **Figure 27** depicts nucleotide sequences corresponding to the 5' untranslated region of human *mcg18*.

- 14 -

Figure 28 depicts a Northern blot showing expression of *mcg18* transcripts in total RNA isolated from various human cancer cell lines grown in culture. Lanes 1-5 respectively contain 15 μ g RNA from H69 lung carcinoma cells, JAM ovary carcinoma cells, BT20 breast carcinoma cells, HaCat transformed keratinocytes, T24 bladder carcinoma cells.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an amino acid sequence having
5 homology to a regulator of gene expression or a derivative of said gene regulator.

More particularly, the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a regulator of gene expression wherein said regulator comprises a zinc finger domain of an $(\text{HC}_3)_2$
10 type.

Still more particularly, the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides or a complementary form thereof selected from:

- 15 (i) a nucleotide sequence set forth in SEQ ID NO:2;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:3;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions at 42°C
20 to the nucleotide sequence set forth in (i), (ii) or (iii).

The present invention also provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an amino acid sequence having homology to a guanine nucleotide exchange factor (GEF) or a derivative thereof.

25

More particularly, the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides or a complementary form thereof selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:4 or 6;
- 30 (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:5 or 7;

- 16 -

- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions at 42°C to the nucleotide sequence set forth in (i), (ii) or (iii).

5

Another aspect of the present invention contemplates an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an amino acid sequence having homology to a heat shock protein or a heat shock-binding protein or a derivative thereof.

10

More particularly, the present invention is directed to an isolated nucleic acid molecule comprising a sequence of nucleotides or a complementary form thereof selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:8;
- 15 (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:9;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridizing under low stringency conditions at 42°C to the nucleotide sequence set forth in (i), (ii) or (iii).

20

Preferably, the percentage similarity is at least about 50%. More preferably, the percentage similarity is at least about 60%.

Reference herein to a low stringency at 42°C includes and encompasses from at least about 1%
25 v/v to at least about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M
30 to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least

- 17 -

about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

The term "similarity" as used herein includes exact identity between compared sequences at the
5 nucleotide or amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational
10 levels.

The present invention extends to nucleic acid molecules with percentage similarities of approximately 65%, 70%, 75%, 80%, 85%, 90% or 95% or above or a percentage in between.

15 The nucleic acid molecule of the present invention defined by SEQ ID NO:2 is hereinafter referred to as constituting the "*mcg4*" gene. The protein encoded by *mcg4* is referred to herein as "MCG4" and has an amino acid sequence set forth in SEQ ID NO:3. The *mcg4* gene is proposed to encode, in accordance with the present invention, a regulator of gene expression and comprises a novel zinc finger domain, $(\text{HC}_3)_2$. A regulator of gene expression includes a
20 transcription factor. Regulation may be at the level of nucleic acid:protein or protein:protein interaction.

The nucleic acid molecule of the present invention defined by SEQ ID NO:4 or 6 is hereinafter referred to as constituting the "*mcg7*" gene. The protein encoded by *mcg7* is referred to herein
25 as "MCG7" and has an amino acid sequence set forth in SEQ ID NO:5 or 7 and is involved in signal transduction. The difference in the nucleotide and amino acid sequence is due to the presence or absence of an exon at nucleotides 183-288.

The nucleic acid molecule of the present invention defined by SEQ ID NO:8 is hereinafter
30 referred to as constituting the "*mcg18*" gene. The protein encoded by *mcg18* is referred to herein as "MCG18" and comprises the amino acid set forth in SEQ ID NO:9.

- 18 -

The present invention extends to the naturally occurring genomic *mcg4*, *mcg7* and *mcg18* nucleotide sequences or corresponding cDNA sequences or to derivatives thereof. Derivatives contemplated in the present invention include fragments, parts, portions, mutants, homologues and analogues of MCG4, MCG7 or MCG8 or the corresponding genetic sequences. Derivatives
5 also include single or multiple amino acid substitutions, deletions and/or additions to MCG4, MCG7 or MCG18 or single or multiple nucleotide substitutions, deletions and/or additions to *mcg4*, *mcg7* or *mcg18*. "Additions" to the amino acid or nucleotide sequences include fusions with other peptides, polypeptides or proteins or fusions to nucleotide sequences. Reference herein to "MCG4" or "*mcg4*", "MCG7" or "*mcg7*" or "MCG8" or *mcg18*" includes reference to
10 all derivatives thereof including functional derivatives and immunologically interactive derivatives of MCG4, MCG7 or MCG18.

The *mcg4*, *mcg7* and *mcg18* of the present invention are particularly exemplified herein from humans and in particular from human chromosome 11q13.

15

The present invention extends, however, to a range of homologues from, for example, primates, livestock animals (eg. sheep, cows, horses, donkeys, pigs), companion animals (eg. dogs, cats) laboratory test animals (eg. rabbits, mice, rats, guinea pigs), reptiles, birds (eg. chickens, ducks, geese, parrots), insects, nematodes, eukaryotic microorganisms and captive wild animals (eg.
20 deer, foxes, kangaroos). Reference herein to *mcg4* and *mcg18* or their respective proteins MCG4, MCG7 and MCG18 includes reference to these molecules of human origin as well as novel forms of non-human origin.

The nucleic acid molecules of the present invention may be DNA or RNA. When the nucleic
25 acid molecule is in DNA form, it may be genomic DNA or cDNA. RNA forms of the nucleic acid molecules of the present invention are generally mRNA.

Although the nucleic acid molecules of the present invention are generally in isolated form, they may be integrated into or ligated to or otherwise fused or associated with other genetic
30 molecules such as vector molecules and in particular expression vector molecules. Vectors and expression vectors are generally capable of replication and, if applicable, expression in one or

- 19 -

both of a prokaryotic cell or a eukaryotic cell. Preferably, prokaryotic cells include *E. coli*, *Bacillus sp* and *Pseudomonas sp*. Preferred eukaryotic cells include yeast, fungal, mammalian and insect cells.

- 5 Accordingly, another aspect of the present invention contemplates a genetic construct comprising a vector portion and an animal, more particularly a mammalian and even more particularly a human *mcg4* gene portion, which *mcg4* gene portion is capable of encoding an MCG4 polypeptide or a functional or immunologically interactive derivative thereof.
- 10 Preferably, the *mcg4* gene portion of the genetic construct is operably linked to a promoter in the vector such that said promoter is capable of directing expression of said *mcg4* gene portion in an appropriate cell.

In addition, the *mcg4* gene portion of the genetic construct may comprise all or part of the gene
15 fused to another genetic sequence such as a nucleotide sequence encoding glutathione-S-transferase or part thereof.

The present invention extends to such genetic constructs and to prokaryotic or eukaryotic cells comprising same.

20

It is proposed in accordance with the present invention that MCG4 is a transcription factor involved in gene regulation. Mutations in *mcg4* may result in aberrations in gene regulation leading to the development of or a propensity to develop various types of cancer. In this regard, although not wishing to limit the present invention to any one hypothesis or mode of action, it
25 is proposed that *mcg4* or its expression product may be involved in the tissue-specific or temporal regulation of particular genes.

A deletion or aberration in the *mcg4* gene may also be important in the detection of cancer or a propensity to develop cancer. An aberration may be a homozygous mutation or a
30 heterozygous mutation. The detection may occur at the foetal or post-natal level. Detection may also be at the germline or somatic cell level. Furthermore, a risk of developing cancer may

be determined by assaying for aberrations in the parents and/or proband of a subject under investigation.

According to this aspect of the present invention, there is contemplated a method of detecting
5 a condition caused or facilitated by an aberration in *mcg4*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg4* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

10

Another aspect of the present invention contemplates a genetic construct comprising a vector portion and an animal, more particularly a mammalian and even more particularly a human *mcg7* gene portion, which *mcg7* gene portion is capable of encoding an *mcg7* polypeptide or a functional or immunologically interactive derivative thereof.

15

Preferably, the *mcg7* gene portion of the genetic construct is operably linked to a promoter on the vector such that said promoter is capable of directing expression of said *mcg7* gene portion in an appropriate cell.

20 In addition, the *mcg7* gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding glutathione-S-transferase or part thereof.

The present invention extends to such genetic constructs and to prokaryotic or eukaryotic cells
25 comprising same.

It is proposed in accordance with the present invention that MCG7 is a GEF involved in signal transduction. Mutations in *mcg7* or MCG7 may result in defective control of cell proliferation leading to the development of or a propensity to develop various types of cancer.

30

A deletion or aberration in the *mcg7* gene may also be important in the detection of cancer or

- 21 -

a propensity to develop cancer. An aberration may be a homozygous mutation or a heterozygous mutation. The detection may occur at the foetal or post-natal level. Detection may also be at the germline or somatic cell level. Furthermore, a risk of developing cancer may be determined by assaying for aberrations in the parents of a subject under investigation.

5

According to this aspect of the present invention, there is contemplated a method of detecting a condition caused or facilitated by an aberration in *mcg7*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg7* wherein the presence of such a nucleotide
10 substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

Yet another aspect of the present invention contemplates a genetic construct comprising a vector portion and an animal, more particularly a mammalian and even more particularly a human
15 *mcg18* gene portion, which *mcg18* gene portion is capable of encoding an MCG18 polypeptide or a functional or immunologically interactive derivative thereof.

Preferably, the *mcg18* gene portion of the genetic construct is operably linked to a promoter on the vector such that said promoter is capable of directing expression of said *mcg18* gene portion
20 in an appropriate cell.

In addition, the *mcg18* gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding glutathione-S-transferase or part thereof.

25

The present invention extends to such genetic constructs and to prokaryotic or eukaryotic cells comprising same.

It is proposed in accordance with the present invention that MCG18 is a transcription factor
30 involved in protein folding, protein complex assembly and transit through subcellular compartments. MCG18 may also have a role in tumour suppression. Thus mutations in *mcg18*

- 22 -

may result in the development of or a propensity to develop various types of cancer.

A deletion or aberration in the *mcg18* gene may also be important in the detection of cancer or a propensity to develop cancer. An aberration may be a homozygous mutation or a
5 heterozygous mutation. The detection may occur at the foetal or post-natal level. Detection may also be at the germline or somatic cell level. Furthermore, a risk of developing cancer may be determined by assaying for aberrations in the parents and/or proband of the subject under investigation.

10 According to this aspect of the present invention, there is contemplated a method of detecting a condition caused or facilitated by an aberration in *mcg18*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other
aberration to one or both alleles of said *mcg18* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or
15 a propensity to develop said condition.

The nucleotide substitutions, additions or deletions may be detected by any convenient means including nucleotide sequencing, restriction fragment length polymorphism (RFLP), polymerase chain reaction (PCR), oligonucleotide hybridization and single stranded conformation
20 polymorphism analysis (SSCP) amongst many others. An aberration includes modification to existing nucleotides such as to modify glycosylation signal amongst other effects.

In an alternative method, aberrations in the *mcg4*, *mcg7* and *mcg18* genes are detected by screening for mutations in MCG4, MCG7 and MCG18, respectively.
25

A mutation in MCG4, MCG7 or MCG18 may be a single or multiple amino acid substitution, addition and/or deletion. The mutation in *mcg4*, *mcg7* or *mcg18* may also result in either no translation product being produced or a product in truncated form. A mutant may also be an altered glycosylation pattern or the introduction of side chain modifications to amino acid
30 residues.

- 23 -

According to this aspect of the present invention, there is provided a method of detecting a condition caused or facilitated by an aberration in *mcg4*, *mcg7* or *mcg18* said method comprising screening for a single or multiple amino acid substitution, deletion and/or addition to MCG4, MCG7 or MCG18 wherein the presence of such a mutation is indicative of or a propensity to
5 develop said condition.

A particularly convenient means of detecting a mutation in MCG4, MCG7 or MCG18 is by use of antibodies.

- 10 Accordingly another aspect of the present invention is directed to antibodies to MCG4, MCG7 or MCG18 and its derivatives. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to MCG4, MCG7 or MCG18 or may be specifically raised to MCG4, MCG7 or MCG18 or derivatives thereof. In the case of the latter, MCG4, MCG7 or MCG18 or their derivatives may first need to be associated with a carrier molecule.
15 The antibodies to MCG4, MCG7 or MCG18 of the present invention are particularly useful as diagnostic agents.

For example, antibodies to MCG4, MCG7 or MCG18 and their derivatives can be used to screen for wild-type MCG4, MCG7 or MCG18 or for mutated MCG4, MCG7 or MCG18 molecules.

- 20 The latter may occur, for example, during or prior to certain cancer development. A differential binding assay is also particularly useful. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of normal MCG4, MCG7 or MCG18 levels or the presence of wild-type MCG4, MCG7 or MCG18 may be important for diagnosis of certain cancers or a predisposition for development of cancers or for monitoring
25 certain therapeutic protocols.

As stated above antibodies to MCG4, MCG7 or MCG18 of the present invention may be monoclonal or polyclonal or may be fragments of antibodies such as Fab fragments. Furthermore, the present invention extends to recombinant and synthetic antibodies and to
30 antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies.

For example, specific antibodies can be used to screen for wild-type MCG4, MCG7 or MCG18 molecule or specific mutant molecules such as molecules having a certain deletion. This would be important, for example, as a means for screening for levels of MCG4, MCG7 or MCG18 in a cell extract or other biological fluid or purifying MCG4, MCG7 or MCG18 made by
5 recombinant means from culture supernatant fluid or purified from a cell extract. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays and ELISA.

It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal
10 or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies discussed above. Both the first and second antibodies may be used in detection assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of wild-type MCG4, MCG7 or MCG18 or to a specific mutant phenotype or to a deleted or otherwise altered region.

15

Both polyclonal and monoclonal antibodies are obtainable by immunization of a suitable animal or bird with MCG4, MCG7 or MCG18 or its derivatives and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively easily prepared by injection of a suitable
20 laboratory animal or bird with an effective amount of MCG4, MCG7 or MCG18 or antigenic parts thereof or derivatives thereof, collecting serum from the animal or bird, and isolating specific sera by any of the known immunoabsorbent techniques. Although antibodies produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

25

The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation can be done by techniques
30 which are well known to those who are skilled in the art.

Another aspect of the present invention contemplates a method for detecting MCG4, MCG7 or MCG18 or a derivative thereof in a biological sample said method comprising contacting said biological sample with an antibody specific for MCG4, MCG7 or MCG18 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG4, MCG7 or
5 MCG18 complex to form, and then detecting said complex.

Preferably, the biological sample is a cell extract from a human or other animal or a bird.

The presence of MCG4, MCG7 or MCG18 may be accomplished in a number of ways such as
10 by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by reference to US Patent Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as traditional competitive binding assays. These assays also include direct binding of a labelled antibody to a target.

15

Sandwich assays are among the most useful and commonly used assays and are favoured for use in the present invention. A number of variations of the sandwich assay technique exist, and all are intended to be encompassed by the present invention. Briefly, in a typical forward assay, an unlabelled antibody is immobilized on a solid substrate and the sample to be tested brought into
20 contact with the bound molecule. After a suitable period of incubation, for a period of time sufficient to allow formation of an antibody-antigen complex, a second antibody specific to the antigen, labelled with a reporter molecule capable of producing a detectable signal is then added and incubated, allowing time sufficient for the formation of another complex of antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the antigen is
25 determined by observation of a signal produced by the reporter molecule. The results may either be qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are added simultaneously to the bound antibody. These techniques are well known to those skilled in the
30 art, including any minor variations as will be readily apparent. In accordance with the present invention the sample is one which might contain MCG4, MCG7 or MCG18 including cell extract

or tissue biopsy. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the MCG4, MCG7
5 or MCG18 or an antigenic part thereof or a derivative thereof or antigenic parts thereof, is either covalently or passively bound to a solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any other surface suitable for conducting an immunoassay. The binding
10 processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more convenient) and under suitable conditions (e.g. from room temperature to 37°C) to allow binding of any subunit present in the
15 antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

20 An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-
25 first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-
30 bound antibody. Detection may be either qualitative or quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide

containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily available to the skilled
5 artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a
10 fluorescent product rather than the chromogenic substrates noted above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated,
15 usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample. "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically
20 coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength, the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the
25 unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

30

As stated above, the present invention extends to genetic constructs capable of encoding MCG4,

MCG7 or MCG18 or functional derivatives thereof. Such genetic constructs are also contemplated to be useful in modulating expression of specific genes in which *mcg4*, *mcg7* or *mcg18* is involved in tissue-specific or temporal regulation.

- 5 Accordingly, another aspect of the present invention is directed to a genetic construct comprising a nucleotide sequence encoding a peptide, polypeptide or protein and *mcg4*, *mcg7* or *mcg18* or a functional derivative or homologue thereof capable of modulating the expression of said nucleotide sequence.
- 10 As stated above, MCG18 is proposed to have a role in tumour suppression. Accordingly, it is further proposed in accordance with the present invention to use recombinant MCG18 in pharmaceutical preparations for treating arresting or otherwise ameliorating the effects of certain cancers.
- 15 Accordingly, another aspect of the present invention contemplates a method for treating, arresting or otherwise ameliorating the effects of a cancer in an animal or bird, said method comprising administering to said animal or bird an effective amount of MCG18 or a functional derivative thereof for a time and under conditions sufficient to treat, arrest or otherwise ameliorate the effects of said cancer.
- 20
- The present invention, therefore, contemplates a pharmaceutical composition comprising MCG18 or a derivative thereof or a modulator of *mcg18* expression or MCG18 activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are referred to hereinafter as the "active ingredients". The active ingredients may also include anti-cancer
- 25 agents or agents which facilitate actions of MCG18.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be

30 preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier may be a solvent medium containing, for example, water, ethanol, polyol (for example,

glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin and by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, 5 chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

- 10 Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired 15 ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with 20 the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 25 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μ g and 2000 mg of active compound.

- 30 The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter. A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium

phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such a sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of
5 the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form
10 should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams,
15 lotions and gels.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known
20 in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease
25 of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the
30 unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the

treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in
5 effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as
hereinbefore disclosed. A unit dosage form can, for example, contain the principal active
compound in amounts ranging from 0.5 μg to about 2000 mg. Expressed in proportions, the
active compound is generally present in from about 0.5 μg to about 2000 mg/ml of carrier. In
the case of compositions containing supplementary active ingredients, the dosages are
10 determined by reference to the usual dose and manner of administration of the said ingredients.

Effective amounts contemplated by the present invention include those amounts effective to
ameliorate a condition. For example, it is envisaged that effective amounts would range from
about 0.001 $\mu\text{g/kg}$ body weight to about 100 mg/kg body weight. Alternatively, effective
15 amounts of about 0.01 $\mu\text{g/kg}$ body weight to about 10 mg/kg body weight or even 0.1 $\mu\text{g/kg}$
body weight to about 1 mg/kg body weight. Administration may be per minute, hour, day, week,
month or year or may only be a once off administration.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable
20 of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating
mcb18 expression or MCG18 activity. The vector may, for example, be a viral vector.

As stated above, the present invention further contemplates a range of derivatives of MCG18.
Derivatives include fragments, parts, portions, mutants, homologues and analogues of the
25 MCG18 polypeptide and corresponding genetic sequence. Derivatives also include single or
multiple amino acid substitutions, deletions and/or additions to MCG18 or single or multiple
nucleotide substitutions, deletions and/or additions to the genetic sequence encoding MCG18.
"Additions" to amino acid sequences or nucleotide sequences include fusions with other
peptides, polypeptides or proteins or fusions to nucleotide sequences. Reference herein to
30 "MCG18" includes reference to all derivatives thereof including functional derivatives or MCG18
immunologically interactive derivatives.

Analogues of MCG18 contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

5

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups
10 with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 .

The guanidine group of arginine residues may be modified by the formation of heterocyclic
15 condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

20 Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and
25 other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides.

Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form
30 a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis
5 include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acids, contemplated herein is shown in Table 3.

TABLE 3

Non-conventional amino acid	Code	Non-conventional amino acid	Code
5			
α -aminobutyric acid	Abu	L-N-methylalanine	Nmala
α -amino- α -methylbutyrate	Mgab	L-N-methylarginine	Nmarg
aminocyclopropane- carboxylate	Cpro	L-N-methylasparagine	Nmasn
		L-N-methylaspartic acid	Nmasp
10 aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbomyl- carboxylate	Norb	L-N-methylglutamine	Nmgln
		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-N-methylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
15 D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Das	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
20 D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
25 D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
30 D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva

	D-tyrosine	Dtyr	α -methyl-aminoisobutyrate	Maib
	D-valine	Dval	α -methyl- γ -aminobutyrate	Mgab
	D- α -methylalanine	Dmala	α -methylcyclohexylalanine	Mchexa
	D- α -methylarginine	Dmarg	α -methylcyclopentylalanine	Mcpen
5	D- α -methylasparagine	Dmasn	α -methyl- α -naphthylalanine	Manap
	D- α -methylaspartate	Dmasp	α -methylpenicillamine	Mpen
	D- α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D- α -methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D- α -methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
10	D- α -methylisoleucine	Dmile	N-amino- α -methylbutyrate	Nmaabu
	D- α -methylleucine	Dmleu	α -naphthylalanine	Anap
	D- α -methyllysine	Dmlys	N-benzylglycine	Nphe
	D- α -methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
	D- α -methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
15	D- α -methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D- α -methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D- α -methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D- α -methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D- α -methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
20	D- α -methyltyrosine	Dmtty	N-cyclodecylglycine	Ncdec
	D- α -methylvaline	Dmval	N-cylcododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
25	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
30	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl)glycine	Nhis
	D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp

	D-N-methyllysine	Dnmlys	N-methyl- γ -aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmt
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpn
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
5	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyl- α -naphthylalanine	Nmanap
10	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ -aminobutyric acid	Gabu	N-(<i>p</i> -hydroxyphenyl)glycine	Nhtyr
	L- <i>t</i> -butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L- α -methylalanine	Mala
15	L- α -methylarginine	Marg	L- α -methylasparagine	Masn
	L- α -methylaspartate	Masp	L- α -methyl- <i>t</i> -butylglycine	Mtbug
	L- α -methylcysteine	Mcys	L-methylethylglycine	Metg
	L- α -methylglutamine	Mgln	L- α -methylglutamate	Mglu
	L- α -methylhistidine	Mhis	L- α -methylhomophenylalanine	Mhphe
20	L- α -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L- α -methyllucine	Mleu	L- α -methyllysine	Mlys
	L- α -methylmethionine	Mmet	L- α -methylnorleucine	Mnle
	L- α -methylnorvaline	Mnva	L- α -methylornithine	Morn
	L- α -methylphenylalanine	Mphe	L- α -methylproline	Mpro
25	L- α -methylserine	Mser	L- α -methylthreonine	Mthr
	L- α -methyltryptophan	Mtrp	L- α -methyltyrosine	Mtyr

- 37 -

L- α -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhph
N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl- 5 ethylamino)cyclopropane	Nmbc		

Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with $n=1$ to $n=6$,
 10 glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example, incorporation of C_α and N_ϵ -methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and
 15 the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

Such analogues also apply in respect of MCG4 and MCG7.

20

The present invention further contemplates chemical analogues of MCG18 capable of acting as antagonists or agonists of MCG18 or which can act as functional analogues of MCG18. Chemical analogues may not necessarily be derived from MCG18 but may share certain conformational similarities. Alternatively, chemical analogues may be specifically designed to
 25 mimic certain physiochemical properties of MCG18. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening.

The identification of MCG18 permits the generation of a range of therapeutic molecules capable of modulating expression of MCG18 or modulating the activity of MCG18. Modulators
 30 contemplated by the present invention includes agonists and antagonists of MCG18 expression. Antagonists of MCG18 expression include antisense molecules, ribozymes and co-suppression

molecules. Agonists include molecules which increase promoter ability or interfere with negative regulatory mechanisms. Agonists of MCG18 include molecules which overcome any negative regulatory mechanism. Antagonists of MCG18 include antibodies and inhibitor peptide fragments.

5

These types of modifications may be important to stabilise MCG18 if administered to an individual or for use as a diagnostic reagent.

Other derivatives contemplated by the present invention include a range of glycosylation variants
10 from a completely unglycosylated molecule to a modified glycosylated molecule. Altered glycosylation patterns may result from expression of recombinant molecules in different host cells.

Another embodiment of the present invention contemplates a method for modulating expression
15 of MCG18 in a human, said method comprising contacting the *mcg18* gene encoding MCG18 with an effective amount of a modulator of *mcg18* expression for a time and under conditions sufficient to up-regulate or down-regulate or otherwise modulate expression of *mcg18*. For example, a nucleic acid molecule encoding MCG18 or a derivative thereof may be introduced into a cell to facilitate protection of that cell from becoming cancerous.

20

Another aspect of the present invention contemplates a method of modulating activity of MCG18 in a human, said method comprising administering to said mammal a modulating effective amount of a molecule for a time and under conditions sufficient to increase or decrease MCG18 activity. The molecule may be a proteinaceous molecule or a chemical entity and may also be a derivative
25 of MCG18 or a chemical analogue or truncation mutant of MCG18.

The present invention is further described with reference to the following non-limiting Examples.

EXAMPLE 1

A human gene (designated *mcg4*) was identified on chromosome 11q13 that on the basis of sequence homology is predicted to encode a putative transcription factor of 310 amino acids (Fig. 1). *mcg4* is transcribed in several different cell lines (Fig. 7).

EXAMPLE 2

The expressed sequence tag (EST) database contains partial sequence data for the murine (Fig. 2) and nematode (Fig. 3) homologues of *mcg4*.

EXAMPLE 3

MCG4 contains a sequence of cysteine residues within the N-terminal region of the protein that resembles zinc-finger binding domains of a novel type, ie. $(HC_3)_2$ [Fig. 4].

EXAMPLE 4

Sensitive sequence homology searches reveal that related cysteine-containing motifs are present in another *C. elegans* protein (Fig. 5) as well as the GATA-binding transcription factor from *S. pombe* (Fig. 6).

EXAMPLE 5

mcg4 will have commercial value due to its likelihood of encoding a novel transcription factor that is highly conserved amongst organisms, thus suggesting an integral role in gene regulation. *mcg4* may also be involved in some way in tissue-specific or temporal regulation of certain genes, thus making it a potential target for modulating expression of those downstream effectors.

EXAMPLE 6

Nucleotide sequence data generated from cosmid clone cSRL-72c4 with the T7 primer (Promega, and Applied Biosystems Incorporated dye terminator sequencing kit) was aligned to
5 the GenBank Expressed Sequence Tag (EST) database using the program BLASTN (Altschul *et al* 1990) and was found to match numerous human and mouse entries (Table 4 and Figure 2). These matching ESTs were further used to identify overlapping entries in the EST database (Table 5). The nucleotide sequences of these human ESTs were compiled using MacVector 4.2.1 software (IBI-Kodak) to produce the cDNA sequence shown in Figure 1. EST entries
10 AA074703 and AA134788 are closely related at the nucleotide level to *mcg4* and it is, therefore, likely that *mcg4* is a member of a newly discovered gene family (Figure 8).

The cDNA sequence of *mcg4* was translated in all possible reading frames and compared to the GenBank non-redundant protein database using the program BLASTX (Altschul *et al*, 1990) at
15 the National Center for Biotechnology Information (<http://www.ncbi.nih.gov.nlm>). As the protein appeared to be novel, a translation of the longest reading frame for the *mcg4* cDNA was aligned to the EST database using the program TBLASTN, which performed a dynamic translation of the EST database in all 6 frames. The search results indicated that the nematode *C. elegans* had an MCG4-like protein (Figure 3), with the matching domains containing a spatial
20 sequence of Cysteine and Histidine residues which resembled a zinc-finger structure (Figure 4). The program BLASTP was used, therefore, to conduct sensitive searches of the protein databases for similar zinc-finger motifs. A weak match to the putative zinc-finger domain was observed for another protein from *C. elegans* (Figure 5) and a poorer match for the GATA-binding transcription factor from *S. pombe* (Figure 6). The putative initiation codon of human
25 *mcg4* is not preceded by an in-frame stop codon and it is therefore possible that the cDNA described in Figure 1 is a truncated form. However, sequence alignment of human and mouse *mcg4* ESTs showed a lower degree of nucleotide conservation prior to the assigned initiation codon, thus supporting the notion that the region represents the 5' UTR (Figure 9). To determine the expression pattern of *mcg4*, 15µg of the total cellular RNA (RNeasy Mini Kit,
30 Qiagen) from various human cell lines grown in culture were electrophoresed through 1.2% w/v MOPS/formaldehyde gels and blotted onto nylon membranes (Amersham) by capillary transfer

- 41 -

using 20 x SSC (Sambrook *et al*, 1989). Filters were subsequently UV-fixed and hybridised overnight at 65°C to a radiolabelled (³²P-dCTP) cDNA probe (Church and Gilbert, 1984) for *mcg4*. After washes in 0.1 x SSC/0.1% w/v SDS at 65°C for 1 hour, the filters were air-dried and exposed to X-ray film. This Northern analysis showed that *mcg4* is expressed as a 1.6kb message in numerous tissues including breast, ovary, bladder, lung and keratinocytes (Figure 7).

EXAMPLE 7

A human gene (designated *mcg7*) was identified and isolated from chromosome 11q13 which encodes a protein that bears striking homology with guanine nucleotide exchange factors (GEFs) from a wide variety of organisms (Fig. 12).

EXAMPLE 8

The composite *mcg7* cDNA sequence is at least 2.4kb in length and Figure 13(a) shows a predicted translation product of at least 609 amino acids beginning at methionine 120. An alternative start site due to alternate exon splicing (indicated in lower case) may yield a protein of 671 amino acids starting at methionine 58 (Fig. 13a).

EXAMPLE 9

An *mcg7* homologue from *C. elegans* has been identified, the product of which is highly conserved with that of MCG7 (Fig. 14). There are several salient features of the protein which have been underlined in Fig. 14 - namely: a guanine nucleotide binding region, a diacylglycerol binding region, and "EF-hand"-calcium binding regions. In addition, there are several potential cAMP, protein kinase C, and casein kinase II phosphorylation sites, as well as a number of potential sites for glycosylation (not indicated).

EXAMPLE 10

A number of partial human and murine EST clones exist for *mcg7*. The GenBank database

contains a cDNA (Acc. no. Y12336) encoding a full-length open reading frame (ORF) for human *mcg7* as well as a partial murine *mcg7* ORF (Y12339). In addition, the complete genomic sequence of the human *mcg7* gene is contained within GenBank entry AC000134.

5

EXAMPLE 11

The best characterised GEFs are members of the family of *ras* oncoproteins, which play a pivotal role in signal transduction and when mutated are responsible for tumour development. A variety of therapeutic regimes for cancer treatment have been designed to specifically interfere with the *ras* signalling pathways. There is potential, therefore that the product of *mcg7* could also be a target for such clinical strategies.

EXAMPLE 12

15 The nucleotide sequence for *mcg7* cDNA was extended 5' with genomic DNA sequence from Genbank accession number AC000134 (positions 1-321) and analysed for additional coding sequence 5' to the putative initiation codon (nt 681-683) (Fig. 16). An additional in-frame ATG occurs at position nt 495-497 when the alternatively splice exon (position nt 504-609) is present (also shown in Fig. 13(a)). This closely matches the Kozak consensus. When this exon is
20 absent, then the ATG is not in-frame and other possible initiation codons are absent (resulting translation shown in lower case lettering) (also shown in Fig. 13(b)). Further evidence that the initiation codon at position nt 681-683 is the true initiation site is given in Figure 15.

Alignment of human and a partial murine *mcg7* cDNA sequences is shown in Figure 15. The
25 putative initiation codon is at position nt 360-362. Both murine ESTs appear to have an upstream in-frame stop codon at position nt 326-328, downstream of the differentially spliced exon and the sequence alignment thus suggests that this region represents the 5' UTR of *mcg7*.

Furthermore, similarity with the *C. elegans* homologue strongly suggest that the ATG codon at
30 position nt 360-362 encodes the N-terminus of MCG7.

EXAMPLE 13

Figure 17 shows data from experiments indicating that a truncated version of MCG7 when expressed as a GST fusion protein (construct B in Fig. 18) can function as a Ras-guanine nucleotide exchange factor. In brief, Ras (unprocessed and as a GST fusion protein) is loaded with ³H-GDP then incubated in the presence of excess cold GTP ± GST-MCG7. Full details of this assay can be found in Porfiri *et al.*

EXAMPLE 14

10

Nucleotide sequence data generated from cosmid clone cSRL-20h12 with the T7 primer (Promega, and Applied Biosystems Incorporated dye terminator sequencing kit) were aligned to the GenBank Expressed Sequence Tag (EST) database using the program BLASTN (Altschul *et al.*, 1990) and was found to match GenBank entries T78563 (clone 113434) TO9103 (clone HIBBP12) and AA035643 (clone 471819). EST clones 113434 and 471819 were obtained from Genome Systems Inc. and these DNAs were sequenced on both strands with gene-specific primers (Table 5) to generate the cDNA sequence of *mcg7* shown in Figures 13(a) and (b).

The cDNA sequence of *mcg7* was translated in all possible reading frames and compared to the GenBank non-redundant protein database using the program BLASTX (Altschul *et al.*, 1990) and the coding region was assigned on the basis of showing homology to the *C. elegans* protein F25B3.3 (Figure 14). The *mcg7* cDNA composite was suspected to contain a single nucleotide error that originated from clone 471819 and the correct nucleotide sequence was, therefore, sought by reverse transcription-polymerase chain reaction (RT-PCR) of the cDNA fragment from a human cDNA pool. Total RNA was extracted from a human lymphoblastoid cell line using an RNeasy Mini Kit (Qiagen). cDNA synthesis was conducted with the reverse transcriptase Superscript II RNaseH- (GIBCO, BRL) and random hexamers using the procedure recommended by the manufacturer (GIBCO, BRL). One fortieth of the cDNA mix was subjected to 35 cycles of PCR using the following cycling conditions: 94°C for 30 seconds, 58°C for 30 seconds and 72°C for 90 seconds. The 50µl reaction mix consisted of 1x reaction buffer (Dade Scientific), 2mM dNTP mix, 20pmol of primers (see Table 6) MCG7UF (within the

variably spliced exon of Figure 13(b), between nucleotide positions 184-201) and SGCADRV2 (between nucleotide positions 866-846 of Figure 13(a)) and 10 units of Dynazyme (Dade Scientific). The resulting PCR product was cloned into the pGEM-T vector (Promega) using standard methodology and sequenced using gene-specific primers. The correct nucleotide sequence of *mcg7* (as shown in Figure 13(a)) matches that of the recently release GenBank entry Y12336. A partial mouse *mcg7* cDNA sequence can also be found in GenBank entry Y12339.

EXAMPLE 15

The coding sequence of *mcg7* was cloned into vectors for expression in both bacterial and mammalian cells. In addition to the full-length constructs, the deletion constructs shown in Figure 18 were designed to retain the guanine nucleotide exchange (GEF) domain. For prokaryotic expression, the *mcg7* coding region was inserted downstream of and in-frame with the Sj26 cassette of the pGEX (Pharmacia) series of vectors (Smith and Johnson, 1988) using standard cloning techniques (Sambrook *et al*, 1989). For mammalian expression, the *mcg7* coding sequence was first *myc*-tagged at the N-terminus and then ligated into the expression vector pc Exv-n using standard cloning techniques. Ligation junctions of the constructs were sequences as the cloning strategies inadvertently changed or introduced additional amino acids as shown below.

20

Construct (A): EST clone 113434 was digested with *Apa*I (Figure 13(a), nucleotide positions 1022 to >2416 (within the vector)), blunt-ended with T4 DNA polymerase according to the specifications of the manufacturer (New England Biolab) and ligated into the *Sma*I site of pGEX-3X.

25

Sequence of the pGEX and *mcg7* (underlined) junction:

pGEX-3X *mcg7* (1022)
Sj26 ... GGG ATC CCC CTG GTC [SEQ ID NO:19]

additional amino acids Gly Ile Pro

30

Construct (B): EST clone 113434 was digested with *Eco*RI (Figure 13(a), nucleotide

pGEX-1 *mcg7* (695)
Sj26 ... GAA TTC GGC ACG AGC CGA CGG [SEQ ID NO:20]
additional amino acids Glu Phe Gly Thr Ser

15 Sequence of the *myc*-tag/*mccg7* junction [SEQ ID NOs:21/22]:

The *myc*-tagged full-length *mcg7* insert in pGEM-11zf was then excised with *SacI* and *HindIII* (both vector derived) and directionally cloned into the mammalian expression vector pEXV
25 (Beranger *et al*, 1994).

Sequence of the pGEX and *mcg7* [SEQ ID NO:23/24] (underlined) junction:

- 46 -

pGEX-2 *Bam*HI *mcg7* (337)
 Sj26 ... gga tcc GCA GCC CAC CCC GCG CCG GCG GCC ATG
 Gly Ser Ala Ala His Pro Ala Pro Ala Ala Met
 -----additional amino acids-----

5

EXAMPLE 16

Overnight bacterial cultures containing the pGEX plasmid were used to inoculate 500ml of Luria Broth media containing 50µg/ml ampicillin. The cultures were grown to an OD of ~0.8 and then
 10 induced with 1mM of IPTG for up to 3 hours at 37°C. The bacteria were pelleted and resuspended in 15 ml of STE buffer (10mM Tris pH 8.0, 150 mM NaCl and 1mM EDTA) with 1 mg/ml lysozyme. The mixture was left on ice for more than 1 hour and subsequent steps were performed at 4°C. Protease inhibitors aprotinin, pepstatin and leupeptin were added at final concentrations of 25µg/ml, prior to the addition of Triton-X-100 (2% v/v final) and n-lauroyl
 15 sarcosine (1.5% w/v final). The lysate was sonicated for ~1 minute and pelleted at 14,000 x g for 15 minutes. 100 µl of 50% w/v glutathione-sephadex bead slurry (in PBS) was added per ml of supernatant. Following a 30 minute incubation at 4°C, the beads were washed three times with NETN (20mM Tris-HCl pH 8.0, 100mM NaCl, 1mM EDTA, 0.5% NP40), once with NETN-HS (equivalent to NETN but with 1M NaCl), and once in NETN. The bound protein
 20 was directly analysed by SDS-polyacrylamide gel electrophoresis (PAGE) as described below or the bound protein was eluted from the beads with the following elution buffer (50mM Tris pH 8.0, 150mM NaCl, 5mM MgCl₂, 1mM DTT, 10mM reduced glutathione) for use in GDP release assays.

25

EXAMPLE 17

Twenty microlitres of GST-sepharose-bound MCG7 were added to an equal volume of 2 x
 30 sample loading dye (100mM Tris pH6.8, 2% v/v mercaptoethanol, 4% w/v SDS, 0.2% w/v bromophenol blue, 20% v/v glycerol), boiled for 5 min and loaded onto a 7.5% w/v SDS-PAGE gel (Sambrook *et al*, 1989). The Coomassie brilliant blue stained gel (Sambrook *et al*, 1989)

typically displayed a protein doublet, running between 87-95 kDa consisting of the MCG7-GST fusion and a slightly smaller, co-purified contaminating *E. coli* protein of ~105kDa. The calculated molecular weight of full-length MCG7 is 77.5 kDa (Construct (D)) and the GST component has a molecular weight of 26kDa, hence, the recombinant protein runs slightly smaller than predicted. A Western blot of the same gel probed with anti-GST antibody yields an MCG7-specific band at the same position as that of the stained gel.

EXAMPLE 18

10 Assumptions: (a) GST-Ras molecular weight = 50 kD; (b) Concentration of GST-Ras solution = 1mg/ml = 20 μ M; (c) [3 H]-GDP is 1mCi/ml and 13.3Ci/mmol, therefore [3 H]-GDP concentration = 75 μ M and 1pmol [3 H]-GDP=15,466 cpm; (d) Elution buffer = Buffer E = 20 mM Tris-Cl, pH7.5; 50mM NaCl; 5mM MgCl₂; 1mM DTT (added just before use). Buffer E + BSA= Buffer E+1mg/ml BSA (added just before use).

15

Mix together, in the following order and mix well after each addition:

10 μ l (=10 μ g) GST-Ras (@ 1mg/ml in Buffer E), 463 μ l Buffer E + BSA, 7 μ l [3 H]-GDP, 10ml 490 μ M EDTA. Incubate @ RT for 10 min. Add 10 μ l 0.5 M MgCl₂ and mix well. Incubate @ RT for 10 min. Place on ice. During the first incubation the excess EDTA concentration is 20 5mM, during the second incubation the excess Mg concentration is 5mM. The [3 H]-GDP concentration is 1 μ M and the final concentration of GST-Ras is 400nM. Thus 20ml of the final mix will contain 8pmol of GST-Ras protein. Specific activity of GDP is 15,446 cpm/pmol x (1/1.4) = 11,047 cpm/pmol.

25

EXAMPLE 19

Exchange Ras with labelled GDP as above. Add unlabelled GTP (stock = 100mM, pH7) to 1 mM. Adjust Mg concentration by adding 5 μ l 0.5 EDTA to labelled Ras, 5 μ l 0.5M EDTA to 500 μ l MCG7, and 5 μ l 0.5M EDTA to 500 μ l Buffer E + BSA. On ice set up microfuge tubes 30 with 40 μ l Ras-GDP (in triplicate) with 40 μ l MCG7 or Buffer E + BSA (control). Transfer tubes to heat block @ 25°C and incubate for 10, 20 or 30 min. Stop exchange reactions with 1ml of

- 48 -

ice cold buffer E and place on ice. Pre-soak nitrocellulose filters, pore size 45 μ m, in Buffer E. Assemble the vacuum manifold apparatus (Millipore) with wet filters and plug the wells with rubber bunds. Switch on the vacuum pump. Remove the first plug, aliquot the sample and once it has been sucked through, wash the filter with 10ml of ice cold Buffer E. Remove next plug
5 etc and continue round the manifold. Take manifold apart. Pin the filters to a pin board reserved for [³H]. Air dry. Take up in 4ml scintillation fluid and count. These studies have been carried out with a truncated MCG7-GST fusion protein (amino acids 341 of Figure 13a to stop encoded within construct B).

10

EXAMPLE 20

A human gene was identified from chromosome 11q13 that encodes a new member of the DnaJ family of proteins (designated MCG18). This gene (*mcg18*) is expressed as an ~1.4kb mRNA (Fig. 28) and is predicted to encode a 241 amino acid product (Fig. 19).

15

EXAMPLE 21

MCG18 has partial homology to *E. coli* dnaJ and other human DnaJ family members in that it contains the J domain (Fig. 20).

20

EXAMPLE 22

MCG18 has greatest homology to functionally undefined proteins from *C. elegans* (Fig. 21) and *S. pombe* (Fig. 22) that also feature the J domain but maintain sequence similarity through the
25 central and C-terminal regions of the proteins.

EXAMPLE 23

The J domain is proposed to mediate interaction with heat shock protein (Hsp70) 70 and consist
30 of some 70 amino acids, frequently located at the N-terminus of the protein. One of these proteins, tumorous imaginal discs (Tid58) from *Drosophila virilis* (Fig. 23) functions as a

tumour suppressor.

EXAMPLE 24

- 5 A comparison of homology between MCG18 and human DnaJ proteins HDJ-2/H5DJ, HDJ-1/HSP40 and HSJ1 is shown in Fig. 24.

EXAMPLE 25

- 10 During the sequence characterisation of the *VRF/VEGFB* promoter region on cosmid CLGW4 [Grimmond *et al*, 1996], which maps to chromosome 11q13 the inventors identified a sequence that exactly matched numerous human and mouse expressed sequence tags (ESTs) in the EST database from a gene which we designated *mcg18*. EST clones for human (GenBank accession number T69741, clone 108172; accession number H40901, clone 177008) and mouse *mcg18*
15 (accession number W34884, clone 350966; accession number W64183, clone 385535) were obtained from Genome Systems Inc. and sequenced with the gene-specific primers shown in Table 7. The EST clones listed in Table 8 were also utilised in generating the full-length coding sequence for human (Figure 19) and mouse (Figure 25) *mcg18*. The EST database also contained *mcg18* cDNA entries that were alternately (or partially) spliced, and in order to
20 understand their ability to encode new polypeptides, the gene structure of *mcg18* was determined by sequencing human and mouse genomic templates with gene-specific primers.

Genomic fragments containing the human [Grimmond *et al*, 1996] and murine genes [Townson *et al*, 1996] have been previously reported. Cosmid CLGW4 contains the entire human gene
25 and λ 121 contains the entire mouse gene, as determined by direct sequencing of the templates with the oligonucleotides listed in Table 7. Plasmids containing sub-fragments of λ 121 and cosmid CLGW4 were prepared using plasmid purification kits (Qiagen) and sequenced as described previously [Grimmond *et al*, 1996; Townson *et al*, 1996] using primers designed against cDNA and genomic sequences. The BLAST suite of programs [Altschul *et al*, 1990]
30 was used to compare the sequence data against the nucleotide and protein databases at the National Center for Biotechnology Information (<http://www.ncbi.nih.gov.nlm>). The sequence

- 50 -

data were compiled using MacVector 4.2.1 software (IBI-Kodak). ClustalW sequence alignments [Thompson *et al*, 1994] were conducted using the Australian National Genome Information Service computer facility at the University of Sydney, Australia.

5 The cDNA sequence of human *mcg18* (Figure 19) was translated in all possible reading frames and compared to the GenBank non-redundant protein database using the program BLASTX [Altschul *et al*, 1990] and the coding region was identified on the basis of showing homology to the DnaJ family of proteins (Figure 20). The DnaJ domain is encoded within the longest open reading frame and the assigned initiation codon is preceded by an in-frame stop codon (Figure
10 27). Similar database search results were obtained for the mouse *mcg18* cDNA, and the alignment of human and mouse protein sequences is shown in Figure 26. MCG18 has greatest homology to gene products from *C. elegans* (Figure 21) and *S. pombe* (Figure 22). Although it shares a similar J-domain, MCG18 does not contain other domains described for the tumour suppressor gene from *D. virilis* (Figure 23), nor is it a homologue of other reported human J-
15 domain-containing proteins (Figure 24).

To determine the expression pattern of *mcg18*, 15µg of total cellular RNA (RNeasy Mini Kit, Qiagen) from various human cell lines grown in culture were electrophoresed through 1.2% MOPS/formaldehyde gels and blotted onto nylon membranes (Amersham) by capillary transfer
20 using 20 x SSC (Sambrook *et al*, 1986). Filters were subsequently UV-fixed and hybridised overnight at 65°C to a radiolabelled (³²P-dCTP) cDNA probe (Church and Gilbert, 1984) for *mcg18*. After washes in 0.1 x SSC/0.1% w/v SDS for 65°C for 1 hour, the filters were air-dried and exposed to X-ray film. This Northern analysis showed that *mcg18* is expressed as a 1.4kb message in numerous tissues including breast, ovary, bladder, lung and keratinocytes (Figure 28).

- 51 -

TABLE 4

ESTs matching *mcg4*

accession number	seq. run	organism	score	E value	N
gb AA399110 AA399110	zt89e06.s1	Soares testis NHT Homo sa...	1136	4.0e-168	2
gb N39612 N39612	yy51g06.s1	Homo sapiens cDNA clone 2...	1521	5.3e-168	4
gb AA514406 AA514406	nf57d01.s1	NCI_CGAP_Co3 Homo sapiens...	931	5.5e-166	3
gb AA544946 AA544946	vk38e02.r1	Soares mouse mammary glan...	1207	8.4e-164	2
gb AA450076 AA450076	zx42a04.s1	Soares total fetus Nb2HF8...	691	2.3e-160	4
gb AA535731 AA535731	nf88f07.s1	NCI_CGAP_Co3 Homo sapiens...	796	3.5e-158	4
gb W79710 W79710	zd86f01.r1	Soares fetal heart NbHH19...	1644	1.1e-157	4
gb AA503531 AA503531	ne47e08.s1	NCI_CGAP_Co3 Homo sapiens...	736	4.0e-156	4
gb AA450132 AA450132	zx42a04.r1	Soares total fetus Nb2HF8...	1955	3.9e-155	1
gb AA398068 AA398068	zt89f06.r1	Soares testis NHT Homo sa...	1315	5.4e-148	2
gb W60405 W60405	zd29h08.r1	Soares fetal heart NbHH19...	1022	1.8e-139	4
gb W81382 W81382	zd86f01.s1	Soares fetal heart NbHH19...	605	3.5e-125	5
gb AA047617 AA047617	zf13f07.s1	Soares fetal heart NbHH19...	922	4.6e-125	2
gb AA282175 AA282175	zt02d03.s1	NCI_CGAP_GCBI Homo sapien...	1577	2.0e-123	1
gb AA242159 AA242159	my30d04.r1	Barstead mouse pooled org...	866	7.7e-117	2
gb AA068680 AA068680	mm61a05.r1	Stratagene mouse embryoni...	1280	1.6e-98	1
gb W46766 W46766	zc36b07.s1	Soares senescent fibrobla...	506	9.6e-92	3
gb N93704 N93704	zb51c04.s1	Soares fetal lung NbHL19W...	584	9.0e-91	4
gb AA155210 AA155210	mr98e01.r1	Stratagene mouse embryoni...	840	7.6e-87	2
gb AA366022 AA366022	EST76915	Pineal gland II Homo sapien...	1077	2.4e-81	1
gb AA037691 AA037691	zk34h12.s1	Soares pregnant uterus Nb...	949	2.1e-80	2
gb W35374 W35374	zc07h03.s1	Soares parathyroid tumor ...	1016	3.1e-76	1
dbj C00696 C00696	HUMGS0008251,	Human Gene Signature, ...	1009	1.2e-75	1
gb T98249 T98249	ye59a07.s1	Homo sapiens cDNA clone 1...	998	6.7e-75	1
gb W21588 W21588	zb51c04.r1	Soares fetal lung NbHL19W...	484	1.1e-69	4
gb H32171 H32171	EST107015	Rattus sp. cDNA 5' end.	828	1.1e-60	1
gb AA108092 AA108092	mm89e06.r1	Stratagene mouse embryoni...	782	1.3e-60	2
gb AA017857 AA017857	mh44d10.r1	Soares mouse placenta 4Nb...	665	2.5e-60	2
gb AA037690 AA037690	zk34h12.r1	Soares pregnant uterus Nb...	540	9.4e-53	2
gb AA531006 AA531006	nj07b11.s1	NCI_CGAP_Pr22 Homo sapien...	535	5.4e-48	2
gb N46760 N46760	yy51g06.r1	Homo sapiens cDNA clone 2...	665	9.5e-47	1
gb W23584 W23584	zc71d03.s1	Soares fetal heart NbHH19...	457	1.8e-44	2
gb W42214 W42214	mc69h09.r1	Soares mouse embryo NbME1...	460	1.3e-38	3
gb AA244877 AA244877	mx25a04.r1	Soares mouse NML Mus musc...	429	2.9e-25	1
gb W32939 W32939	zc07h03.r1	Soares parathyroid tumor ...	320	4.8e-18	1

- 52 -

TABLE 5
ESTs matching AA074703 (*mcg4*-related cDNA)

Database: Non-redundant Database of GenBank EST Division
 1,222,625 sequences; 449,352,662 total letters.

			Smallest		
			Sum		
			High Probability		
Sequences producing High-scoring Segment Pairs:			Score	P(N)	N
accession number	seq. run	organism	score	E value	N
gb AA074703 AA074703	zm76g07.r1	Stratagene neuroepitheli...	2071	4.0e-167	1
gb AA068680 AA068680	mm61a05.r1	Stratagene mouse embryon...	1270	4.4e-145	4
gb AA134788 AA134788	zm81g02.r1	Stratagene neuroepitheli...	946	1.3e-144	5
gb AA399110 AA399110	zt89e06.s1	Soares testis NHT Homo s...	520	8.7e-119	6
gb N39612 N39612	yy51g06.s1	Homo sapiens cDNA clone ...	582	9.6e-110	7
gb AA282175 AA282175	zt02d03.s1	NCI_CGAP_GCB1 Homo sapie...	771	9.4e-80	3
gb W81382 W81382	zd86f01.s1	Soares fetal heart NbHH1...	329	1.6e-75	6
gb AA544946 AA544946	vk38e02.r1	Soares mouse mammary gla...	644	9.6e-63	2
gb W35374 W35374	zc07h03.s1	Soares parathyroid tumor...	294	4.5e-42	4
gb W57106 W57106	md57c12.r1	Soares mouse embryo NbME...	394	1.9e-30	2
gb AA244877 AA244877	mx25a04.r1	Soares mouse NML Mus mus...	162	2.1e-27	4
gb AA017857 AA017857	mh44d10.r1	Soares mouse placenta 4N...	230	3.7e-23	3
gb AA531006 AA531006	nj07b11.s1	NCI_CGAP_Pr22 Homo sapie...	139	2.3e-19	3
gb H32171 H32171	EST107015	Rattus sp. cDNA 5' end.	207	2.6e-10	2
gb W79710 W79710	zd86f01.r1	Soares fetal heart NbHH1...	157	0.0073	1

TABLE 6
***mcg7*-specific oligonucleotides**

5	name	sequence (5' to 3')	SEQ ID NOs.
	M1044R	GGA CAA AGT GTG TGA TGA ACC	SEQ ID NO:25
	MCG7-GEF-REV2	CTC ATC CTC CGT CTG ATA CTG	SEQ ID NO:26
	M7R	GTA GAT GTG GAT CAG CTT GG	SEQ ID NO:27
	MCG7 CA FOR	AGG TGG AGA ATG GTC AAGG	SEQ ID NO:28
10	MCG7-GEF-REV	GTC ATA GTC TGT CTC CTA CT	SEQ ID NO:29
	MCG7 GEF FOR	ACA TAG ACA GCG TGC CTA CC	SEQ ID NO:30
	MCG7-PKC-REV	TAC AAC CTT AGG GAC ACC AG	SEQ ID NO:31
	MCG7-PKC-FOR	TGC TGA GCC TGC TCA CGG TG	SEQ ID NO:32
	T09103F	CAA GTG AAC AGC ACG TCC	SEQ ID NO:33
15	M7F	GAC TAT CTC AAG GAC CAG CTG	SEQ ID NO:34
	MCG7UF	GGT TCG GTC CGA GCC CGG	SEQ ID NO:35
	SGCADRV2	GGA GCG ATA CTC CAA GTA GGT	SEQ ID NO:36

TABLE 7
***mcg18*-SPECIFIC OLIGONUCLEOTIDES**

	name	sequence 5' to 3'
5	HVESTF	AGC GGG CCA GGC CCC TTC [SEQ ID NO:37]
	HV195F	CAT CCT GGT CCA ATG CGC TC [SEQ ID NO:38]
	HV387F2	GCA CTG AGG AAG TTA AAC GAG C [SEQ ID NO:39]
	HV408R	GCT CGT TTA ACT TCC TCA GTG C [SEQ ID NO:40]
	EXON1REV	GCT CAG CTC CAC AAA GCG GCT [SEQ ID NO:41]
10	HVEST426F	ACC AGC TCC GCT CAG GTA G [SEQ ID NO:42]
	HVEST623R	TCC AGG AGC TGT GTG TTT GG [SEQ ID NO:43]
	SGVESTF3	CCA GTT TCA CAG CGT GAG G [SEQ ID NO:44]
	HVEST631R	CAG CAT GAG GAG GAG GCA G [SEQ ID NO:45]

TABLE 8
EST CLONE SEQUENCES USED TO GENERATE HUMAN AND MOUSE
***mcg18* cDNA SEQUENCE COMPOSITES**

<u>EST clone number</u>	<u>organism</u>	<u>GenBank accession number</u>
1g2815	human	D45683
001-T2-18	human	F17225
273748	human	N37043
177008	human	H40901 and H40939
258011	human	N30776
276887	human	N44004
108172	human	T69741
307529	human	W21083 and W32579
342027	human	W60283
354288	mouse	W44038
350966	mouse	W348844
426261	mouse	AA002868
368185	mouse	W53911
385535	mouse	W64183
404472	mouse	W82959
406437	mouse	W83482

BIBLIOGRAPHY

1. Altschul, S.F., Gish, W., Miller, W., Myers, E.W., and Lipman, D.J. (1990) *J. Mol. Biol.* 215: 403-410.
2. Church, G., and Gilbert, W. (1984) *Proc. Natl. Acad. Sci. USA* 18: 1991-1995.
3. Porfiri *et al.* *J. Biol. Chem.* 269: 22672-22677 (1994).
4. Sambrook, J., Fritsch, E.F., and Maniatis, T. (1989) *Molecular Cloning. A Laboratory Manual*. Cold Spring Harbour Laboratory, Cold Spring Harbour, NY, USA.
5. Smith, D.B., and Johnson, K.S. (1988) *Gene* 67: 31-40.
6. Thompson, J.D., Higgins, D.G., and Gibson, T.J. (1994) *Nucleic Acids Res.* 22: 4673-4680.
7. Beranger, F., Paterson, H., Powers, S., de Gunzburg, J. and Hancock, J.F. (1994) *Molecular and Cellular Biology* 14: 744-758.
8. Grimmond, S., Lagercrantz, J., Drinkwater, C., Silins, G., Townson, S., Pollock, P., Gotley, D., Carson, E., Rakar, S., Nordenskjöld, M., Ward, L., Hayward, N., and Weber, G (1996) *Genome Res.* 6: 124-131.
9. Townson, S., Lagercrantz, J., Grimmond, S., Silins, G., Nordenskjöld, Weber, G., and Hayward, N. (1996) *Biochem. Biophys. Res. Commun.* 220: 922-928.

- 57 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: (OTHER THAN US): The Council of The Queensland Institute of
Medical Research
(US ONLY): HAYWARD Nicholas, SILINS Ginters, GRIMMOND Sean,
GARTSIDE Michael and HANCOCK, John

(ii) TITLE OF INVENTION: A NOVEL GENE AND USES THEREFOR

(iii) NUMBER OF SEQUENCES: 45

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: DAVIES COLLISON CAVE
(B) STREET: 1 LITTLE COLLINS STREET
(C) CITY: MELBOURNE
(D) STATE: VICTORIA
(E) COUNTRY: AUSTRALIA
(F) ZIP: 3000

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: PCT INTERNATIONAL
(B) FILING DATE: 22-MAY-1998
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PO6973
(B) FILING DATE: 23-MAY-1997
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PO6974
(B) FILING DATE: 23-MAY-1997
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PO6972
(B) FILING DATE: 23-MAY-1997

- 58 -

(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PP1459

(B) FILING DATE: 22-JAN-1998

(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PP1460

(B) FILING DATE: 22-JAN-1998

(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: PP1458

(B) FILING DATE: 22-JAN-1998

(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: HUGHES, DR E JOHN L

(C) REFERENCE/DOCKET NUMBER: EJH/AF

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: +61 3 9254 2777

(B) TELEFAX: +61 3 9254 2770

(C) TELEX: AA 31787

- 59 -

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 8 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Cys Xaa Xaa Cys Xaa Gly Xaa Gly
 5

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1242 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 30..959

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TCAGTAAACA CAGAGACTGG GGATCGATC	ATG GGG CTT TGT AAG TGC CCC AAG	53
	Met Gly Leu Cys Lys Cys Pro Lys	
	1 5	
AGA AAG GTG ACC AAC CTG TTC TGC TTC GAA CAT CGG GTC AAC GTC TGC	101	
Arg Lys Val Thr Asn Leu Phe Cys Phe Glu His Arg Val Asn Val Cys		
10 15 20		
GAG CAC TGC CTG GTA GCC AAT CAC GCC AAG TGC ATC GTC CAG TCC TAC	149	
Glu His Cys Leu Val Ala Asn His Ala Lys Cys Ile Val Gln Ser Tyr		
25 30 35 40		
CTG CAA TGG CTC CAA GAT AGC GAC TAC AAC CCC AAT TGC CGC CTG TGC	197	
Leu Gln Trp Leu Gln Asp Ser Asp Tyr Asn Pro Asn Cys Arg Leu Cys		
45 50 55		
AAC ATA CCC CTG GCC AGC CGA GAG ACG ACC CGC CTT GTC TGC TAT GAT	245	
Asn Ile Pro Leu Ala Ser Arg Glu Thr Thr Arg Leu Val Cys Tyr Asp		
60 65 70		
CTC TTT CAC TGG GCC TGC CTC AAT GAA CGT GCT GCC CAG CTA CCC CGA	293	
Leu Phe His Trp Ala Cys Leu Asn Glu Arg Ala Ala Gln Leu Pro Arg		
75 80 85		
AAC ACG GCA CCT GCC GGC TAT CAG TGC CCC AGC TGC AAT GGC CCC ATC	341	
Asn Thr Ala Pro Ala Gly Tyr Gln Cys Pro Ser Cys Asn Gly Pro Ile		
90 95 100		
TTC CCC CCA ACC AAC CTG GCT GGC CCC GTG GCC TCC GCA CTG AGA GAG	389	
Phe Pro Pro Thr Asn Leu Ala Gly Pro Val Ala Ser Ala Leu Arg Glu		
105 110 115 120		

- 60 -

AAG CTG GCC ACA GTC AAC TGG GCC CGG GCA GGA CTG GGC CTC CCT CTG	437
Lys Leu Ala Thr Val Asn Trp Ala Arg Ala Gly Leu Gly Leu Pro Leu	
125 130 135	
ATC GAT GAG GTG GTG AGC CCA GAG CCC GAG CCC CTC AAC ACG TCT GAC	485
Ile Asp Glu Val Val Ser Pro Glu Pro Glu Pro Leu Asn Thr Ser Asp	
140 145 150	
TTC TCT GAC TGG TCT AGT TTT AAT GCC AGC AGT ACC CCT GGA CCA GAG	533
Phe Ser Asp Trp Ser Ser Phe Asn Ala Ser Ser Thr Pro Gly Pro Glu	
155 160 165	
GAG GTA GAC AGC GCC TCT GCT GCC CCA GCC TTC TAC AGC CGA GCC CCC	581
Glu Val Asp Ser Ala Ser Ala Ala Pro Ala Phe Tyr Ser Arg Ala Pro	
170 175 180	
CGG CCC CCA GCT TCC CCA GGC CGG CCC GAG CAG CAC ACA GTG ATC CAC	629
Arg Pro Pro Ala Ser Pro Gly Arg Pro Glu Gln His Thr Val Ile His	
185 190 195 200	
ATG GGC AAT CCT GAG CCC TTG ACT CAC GCC CCT AGG AAG GTG TAT GAT	677
Met Gly Asn Pro Glu Pro Leu Thr His Ala Pro Arg Lys Val Tyr Asp	
205 210 215	
ACG CGG GAT GAT GAC CGG ACA CCA GGC CTC CAT GGA GAC TGT GAC GAT	725
Thr Arg Asp Asp Asp Arg Thr Pro Gly Leu His Gly Asp Cys Asp Asp	
220 225 230	
GAC AAG TAC CGA CGT CGG CCG GCC TTG GGT TGG CTG GCC CGG CTG CTA	773
Asp Lys Tyr Arg Arg Arg Pro Ala Leu Gly Trp Leu Ala Arg Leu Leu	
235 240 245	
AGG AGC CGG GCT GGG TCT CGG AAG CGG CCG CTG ACC CTG CTC CAG CGG	821
Arg Ser Arg Ala Gly Ser Arg Lys Arg Pro Leu Thr Leu Leu Gln Arg	
250 255 260	
GCG GGG CTG CTG CTA CTC TTG GGA CTG CTG GGC TTC CTG GCC CTC CTT	869
Ala Gly Leu Leu Leu Leu Leu Gly Leu Leu Gly Phe Leu Ala Leu Leu	
265 270 275 280	
GCC CTC ATG TCT CGC CTA GGC CGG GCC GCA GCT GAC AGC GAT CCC AAC	917
Ala Leu Met Ser Arg Leu Gly Arg Ala Ala Ala Asp Ser Asp Pro Asn	
285 290 295	
CTG GAC CCA CTC ATG AAC CCT CAC ATC CGC GTG GGC CCC TCC TGA	962
Leu Asp Pro Leu Met Asn Pro His Ile Arg Val Gly Pro Ser *	
300 305 310	
GCCCCCTTGC TTGTGGCTAG GCCAGCCTAG GATGTGGGTT CTGTGGAGGA GAGGCGGGGT	1022
AATGGGGAGG CTGAGGGCAC CTCTTCACTG CCCCTCTCCC TCAAGCCTAA GACACTAAGA	1082
CCCCAGACCC AAAGCCAAGT CCACCAGAGT GGCTCGCAGG CCAGGCCTGG AGTCCCCGTG	1142
GGTCAAGCAT TTGTCTTGAC TTGCTTTCTC CCGGGTCTCC AGCCTCCGAC CCCTCGCCCC	1202
ATGAAGGAGC TGGCAGGTGG AAATAAACAA CAACTTTATT	1242

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 310 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

- 61 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Gly Leu Cys Lys Cys Pro Lys Arg Lys Val Thr Asn Leu Phe Cys
 1 5 10 15
 Phe Glu His Arg Val Asn Val Cys Glu His Cys Leu Val Ala Asn His
 20 25 30
 Ala Lys Cys Ile Val Gln Ser Tyr Leu Gln Trp Leu Gln Asp Ser Asp
 35 40 45
 Tyr Asn Pro Asn Cys Arg Leu Cys Asn Ile Pro Leu Ala Ser Arg Glu
 50 55 60
 Thr Thr Arg Leu Val Cys Tyr Asp Leu Phe His Trp Ala Cys Leu Asn
 65 70 75 80
 Glu Arg Ala Ala Gln Leu Pro Arg Asn Thr Ala Pro Ala Gly Tyr Gln
 85 90 95
 Cys Pro Ser Cys Asn Gly Pro Ile Phe Pro Pro Thr Asn Leu Ala Gly
 100 105 110
 Pro Val Ala Ser Ala Leu Arg Glu Lys Leu Ala Thr Val Asn Trp Ala
 115 120 125
 Arg Ala Gly Leu Gly Leu Pro Leu Ile Asp Glu Val Val Ser Pro Glu
 130 135 140
 Pro Glu Pro Leu Asn Thr Ser Asp Phe Ser Asp Trp Ser Ser Phe Asn
 145 150 155 160
 Ala Ser Ser Thr Pro Gly Pro Glu Glu Val Asp Ser Ala Ser Ala Ala
 165 170 175
 Pro Ala Phe Tyr Ser Arg Ala Pro Arg Pro Pro Ala Ser Pro Gly Arg
 180 185 190
 Pro Glu Gln His Thr Val Ile His Met Gly Asn Pro Glu Pro Leu Thr
 195 200 205
 His Ala Pro Arg Lys Val Tyr Asp Thr Arg Asp Asp Arg Thr Pro
 210 215 220
 Gly Leu His Gly Asp Cys Asp Asp Asp Lys Tyr Arg Arg Arg Pro Ala
 225 230 235 240
 Leu Gly Trp Leu Ala Arg Leu Leu Arg Ser Arg Ala Gly Ser Arg Lys
 245 250 255
 Arg Pro Leu Thr Leu Leu Gln Arg Ala Gly Leu Leu Leu Leu Gly
 260 265 270
 Leu Leu Gly Phe Leu Ala Leu Leu Ala Leu Met Ser Arg Leu Gly Arg
 275 280 285
 Ala Ala Ala Asp Ser Asp Pro Asn Leu Asp Pro Leu Met Asn Pro His
 290 295 300
 Ile Arg Val Gly Pro Ser
 305 310

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- 62 -

(A) LENGTH: 2415 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 3..2188

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CG ATT TCA TTC CTC GCT CCC CAC AGG TCC CTC TCC CCA AAA TAT TCC	47
Ile Ser Phe Leu Ala Pro His Arg Ser Leu Ser Pro Lys Tyr Ser	
1 5 10 15	
CAT CTT GTC CTA GCC CAT CCC CCA GAC TAT CTC AAG GAC CAG CTG TCC	95
His Leu Val Leu Ala His Pro Pro Asp Tyr Leu Lys Asp Gln Leu Ser	
20 25 30	
CCA CGC CCC CGA CCT CCA CTA GGC CTG TGC CAC CCG CTG CCT GCA GGA	143
Pro Arg Pro Arg Pro Pro Leu Gly Leu Cys His Pro Leu Pro Ala Gly	
35 40 45	
AGA CGC CCG GTC CCG GGC CGG GTT AGC CCC ATG GGA ACG CAG CGC CTG	191
Arg Arg Pro Val Pro Gly Arg Val Ser Pro Met Gly Thr Gln Arg Leu	
50 55 60	
TGT GGC CGC GGG ACT CAA GGC TGG CCT GGC TCA AGT GAA CAG CAC GTC	239
Cys Gly Arg Gly Thr Gln Gly Trp Pro Gly Ser Ser Glu Gln His Val	
65 70 75	
CAG GAG GCG ACC TCG TCC GCG GGT TTG CAT TCT GGG GTG GAC GAG CTG	287
Gln Glu Ala Thr Ser Ser Ala Gly Leu His Ser Gly Val Asp Glu Leu	
80 85 90 95	
GGG GTT CGG TCC GAG CCC GGT GGG AGG CTC CCG GAG CGC AGC CTG GGC	335
Gly Val Arg Ser Glu Pro Gly Gly Arg Leu Pro Glu Arg Ser Leu Gly	
100 105 110	
CCA GCC CAC CCC GCG CCG GCG GCC ATG GCA GGC ACC CTG GAC CTG GAC	383
Pro Ala His Pro Ala Pro Ala Ala Met Ala Gly Thr Leu Asp Leu Asp	
115 120 125	
AAG GGC TGC ACG GTG GAG GAG CTG CTC CGC GGG TGC ATC GAA GCC TTC	431
Lys Gly Cys Thr Val Glu Glu Leu Leu Arg Gly Cys Ile Glu Ala Phe	
130 135 140	
GAT GAC TCC GGG AAG GTG CGG GAC CCG CAG CTG GTG CGC ATG TTC CTC	479
Asp Asp Ser Gly Lys Val Arg Asp Pro Gln Leu Val Arg Met Phe Leu	
145 150 155	
ATG ATG CAC CCC TGG TAC ATC CCC TCC TCT CAG CTG GCG GCC AAG CTG	527
Met Met His Pro Trp Tyr Ile Pro Ser Ser Gln Leu Ala Ala Lys Leu	
160 165 170 175	
CTC CAC ATC TAC CAA CAA TCC CGG AAG GAC AAC TCC AAT TCC CTG CAG	575
Leu His Ile Tyr Gln Gln Ser Arg Lys Asp Asn Ser Asn Ser Leu Gln	
180 185 190	
GTG AAA ACG TGC CAC CTG GTC AGG TAC TGG ATC TCC GCC TTC CCA GCG	623
Val Lys Thr Cys His Leu Val Arg Tyr Trp Ile Ser Ala Phe Pro Ala	
195 200 205	

GAG TTT GAC TTG AAC CCG GAG TTG GCT GAG CAG ATC AAG GAG CTG AAG Glu Phe Asp Leu Asn Pro Glu Leu Ala Glu Gln Ile Lys Glu Leu Lys 210 215 220	671
GCT CTG CTA GAC CAA GAA GGG AAC CGA CGG CAC AGC AGC CTA ATC GAC Ala Leu Leu Asp Gln Glu Gly Asn Arg Arg His Ser Ser Leu Ile Asp 225 230 235	719
ATA GAC AGC GTC CCT ACC TAC AAG TGG AAG CGG CAG GTG ACT CAG CGG Ile Asp Ser Val Pro Thr Tyr Lys Trp Lys Arg Gln Val Thr Gln Arg 240 245 250 255	767
AAC CCT GTG GGA CAG AAA AAG CGC AAG ATG TCC CTG TTG TTT GAC CAC Asn Pro Val Gly Gln Lys Lys Arg Lys Met Ser Leu Leu Phe Asp His 260 265 270	815
CTG GAG CCC ATG GAG CTG GCG GAG CAT CTC ACC TAC TTG GAG TAT CGC Leu Glu Pro Met Glu Leu Ala Glu His Leu Thr Tyr Leu Glu Tyr Arg 275 280 285	863
TCC TTC TGC AAG ATC CTG TTT CAG GAC TAT CAC AGT TTC GTG ACT CAT Ser Phe Cys Lys Ile Leu Phe Gln Asp Tyr His Ser Phe Val Thr His 290 295 300	911
GGC TGC ACT GTG GAC AAC CCC GTC CTG GAG CGG TTC ATC TCC CTC TTC Gly Cys Thr Val Asp Asn Pro Val Leu Glu Arg Phe Ile Ser Leu Phe 305 310 315	959
AAC AGC GTC TCA CAG TGG GTG CAG CTC ATG ATC CTC AGC AAA CCC ACA Asn Ser Val Ser Gln Trp Val Gln Leu Met Ile Leu Ser Lys Pro Thr 320 325 330 335	1007
GCC CCG CAG CGG GCC CTG GTC ATC ACA CAC TTT GTC CAC GTG GCG GAG Ala Pro Gln Arg Ala Leu Val Ile Thr His Phe Val His Val Ala Glu 340 345 350	1055
AAG CTG CTA CAG CTG CAG AAC TTC AAC ACG CTG ATG GCA GTG GTC GGG Lys Leu Leu Gln Leu Gln Asn Phe Asn Thr Leu Met Ala Val Val Gly 355 360 365	1103
GGC CTG AGC CAC AGC TCC ATC TCC CGC CTC AAG GAG ACC CAC AGC CAC Gly Leu Ser His Ser Ser Ile Ser Arg Leu Lys Glu Thr His Ser His 370 375 380	1151
GTT AGC CCT GAG ACC ATC AAG CTC TGG GAG GGT CTC ACG GAA CTA GTG Val Ser Pro Glu Thr Ile Lys Leu Trp Glu Gly Leu Thr Glu Leu Val 385 390 395	1199
ACG GCG ACA GGC AAC TAT GGC AAC TAC CGG CGT CGG CTG GCA GCC TGT Thr Ala Thr Gly Asn Tyr Gly Asn Tyr Arg Arg Arg Leu Ala Ala Cys 400 405 410 415	1247
GTG GGC TTC CGC TTC CCG ATC CTG GGT GTG CAC CTC AAG GAC CTG GTG Val Gly Phe Arg Phe Pro Ile Leu Gly Val His Leu Lys Asp Leu Val 420 425 430	1295
GCC CTG CAG CTG GCA CTG CCT GAC TGG CTG GAC CCA GCC CGG ACC CGG Ala Leu Gln Leu Ala Leu Pro Asp Trp Leu Asp Pro Ala Arg Thr Arg 435 440 445	1343
CTC AAC GGG GCC AAG ATG AAG CAG CTC TTT AGC ATC CTG GAG GAG CTG Leu Asn Gly Ala Lys Met Lys Gln Leu Phe Ser Ile Leu Glu Glu Leu 450 455 460	1391
GCC ATG GTG ACC AGC CTG CGG CCA CCA GTA CAG GCC AAC CCC GAC CTG Ala Met Val Thr Ser Leu Arg Pro Pro Val Gln Ala Asn Pro Asp Leu 465 470 475	1439

CTG Leu	AGC Ser	CTG Leu	CTC Leu	ACG Thr	GTG Val	TCT Ser	CTG Leu	GAT Asp	CAG Gln	TAT Tyr	CAG Gln	ACG Thr	GAG Glu	GAT Asp	GAG Glu		1487
480					485					490					495		
CTG Leu	TAC Tyr	CAG Gln	CTG Leu	TCC Ser	CTG Leu	CAG Gln	CGG Arg	GAG Glu	CCG Pro	CGC Arg	TCC Ser	AAG Lys	TCC Ser	TCG Ser	CCA Pro		1535
				500					505					510			
ACC Thr	AGC Ser	CCC Pro	ACG Thr	AGT Ser	TGC Cys	ACC Thr	CCA Pro	CCA Pro	CCC Pro	CGG Arg	CCC Pro	CCG Pro	GTA Val	CTG Leu	GAG Glu		1583
			515					520					525				
GAG Glu	TGG Trp	ACC Thr	TCG Ser	GCT Ala	GCC Ala	AAA Lys	CCC Pro	AAG Lys	CTG Leu	GAT Asp	CAG Gln	GCC Ala	CTC Leu	GTG Val	GTG Val		1631
		530					535					540					
GAG Glu	CAC His	ATC Ile	GAG Glu	AAG Lys	ATG Met	GTG Val	GAG Glu	TCT Ser	GTG Val	TTC Phe	CGG Arg	AAC Asn	TTT Phe	GAC Asp	GTC Val		1679
	545					550					555						
GAT Asp	GGG Gly	GAT Asp	GGC Gly	CAC His	ATC Ile	TCA Ser	CAG Gln	GAA Glu	GAA Glu	TTC Phe	CAG Gln	ATC Ile	ATC Ile	CGT Arg	GGG Gly		1727
560					565					570					575		
AAC Asn	TTC Phe	CCT Pro	TAC Tyr	CTC Leu	AGC Ser	GCC Ala	TTT Phe	GGG Gly	GAC Asp	CTC Leu	GAC Asp	CAG Gln	AAC Asn	CAG Gln	GAT Asp		1775
				580					585					590			
GGC Gly	TGC Cys	ATC Ile	AGC Ser	AGG Arg	GAG Glu	GAG Glu	ATG Met	GTT Val	TCC Ser	TAT Tyr	TTC Phe	CTG Leu	CGC Arg	TCC Ser	AGC Ser		1823
			595					600					605				
TCT Ser	GTG Val	TTG Leu	GGG Gly	GGG Gly	CGC Arg	ATG Met	GGC Gly	TTC Phe	GTA Val	CAC His	AAC Asn	TTC Phe	CAG Gln	GAG Glu	AGC Ser		1871
		610					615					620					
AAC Asn	TCC Ser	TTG Leu	CGC Arg	CCC Pro	GTC Val	GCC Ala	TGC Cys	CGC Arg	CAC His	TGC Cys	AAA Lys	GCC Ala	CTG Leu	ATC Ile	CTG Leu		1919
	625					630					635						
GGC Gly	ATC Ile	TAC Tyr	AAG Lys	CAG Gln	GGC Gly	CTC Leu	AAA Lys	TGC Cys	CGA Arg	GCC Ala	TGT Cys	GGA Gly	GTG Val	AAC Asn	TGC Cys		1967
640					645					650					655		
CAC His	AAG Lys	CAG Gln	TGC Cys	AAG Lys	GAT Asp	CGC Arg	CTG Leu	TCA Ser	GTT Val	GAG Glu	TGT Cys	CGG Arg	CGC Arg	AGG Arg	GCC Ala		2015
				660					665					670			
CAG Gln	AGT Ser	GTG Val	AGC Ser	CTG Leu	GAG Glu	GGG Gly	TCT Ser	GCA Ala	CCC Pro	TCA Ser	CCC Pro	TCA Ser	CCC Pro	ATG Met	CAC His		2063
			675					680					685				
AGC Ser	CAC His	CAT His	CAC His	CGC Arg	GCC Ala	TTC Phe	AGC Ser	TTC Phe	TCT Ser	CTG Leu	CCC Pro	CGC Arg	CCT Pro	GGC Gly	AGG Arg		2111
		690					695					700					
CGA Arg	GGC Gly	TCC Ser	AGG Arg	CCT Pro	CCA Pro	GAG Glu	ATC Ile	CGT Arg	GAG Glu	GAG Glu	GAG Glu	GTA Val	CAG Gln	ACG Thr	GTG Val		2159
	705					710					715						
GAG Glu	GAT Asp	GGG Gly	GTG Val	TTT Phe	GAC Asp	ATC Ile	CAC 										

- 65 -

CAGGGCTGGT GTCCCTAAGG TTGTACAGAC TCTTGTGAAT ATTTGTATTT TCCAGATGGA 2388
 ATAAAAAGGC CCGTGTAATT AACCTTC 2415

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 728 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Ile Ser Phe Leu Ala Pro His Arg Ser Leu Ser Pro Lys Tyr Ser His
 1 5 10 15
 Leu Val Leu Ala His Pro Pro Asp Tyr Leu Lys Asp Gln Leu Ser Pro
 20 25 30
 Arg Pro Arg Pro Pro Leu Gly Leu Cys His Pro Leu Pro Ala Gly Arg
 35 40 45
 Arg Pro Val Pro Gly Arg Val Ser Pro Met Gly Thr Gln Arg Leu Cys
 50 55 60
 Gly Arg Gly Thr Gln Gly Trp Pro Gly Ser Ser Glu Gln His Val Gln
 65 70 75 80
 Glu Ala Thr Ser Ser Ala Gly Leu His Ser Gly Val Asp Glu Leu Gly
 85 90 95
 Val Arg Ser Glu Pro Gly Gly Arg Leu Pro Glu Arg Ser Leu Gly Pro
 100 105 110
 Ala His Pro Ala Pro Ala Ala Met Ala Gly Thr Leu Asp Leu Asp Lys
 115 120 125
 Gly Cys Thr Val Glu Glu Leu Leu Arg Gly Cys Ile Glu Ala Phe Asp
 130 135 140
 Asp Ser Gly Lys Val Arg Asp Pro Gln Leu Val Arg Met Phe Leu Met
 145 150 155 160
 Met His Pro Trp Tyr Ile Pro Ser Ser Gln Leu Ala Ala Lys Leu Leu
 165 170 175
 His Ile Tyr Gln Gln Ser Arg Lys Asp Asn Ser Asn Ser Leu Gln Val
 180 185 190
 Lys Thr Cys His Leu Val Arg Tyr Trp Ile Ser Ala Phe Pro Ala Glu
 195 200 205
 Phe Asp Leu Asn Pro Glu Leu Ala Glu Gln Ile Lys Glu Leu Lys Ala
 210 215 220
 Leu Leu Asp Gln Glu Gly Asn Arg Arg His Ser Ser Leu Ile Asp Ile
 225 230 235 240
 Asp Ser Val Pro Thr Tyr Lys Trp Lys Arg Gln Val Thr Gln Arg Asn
 245 250 255
 Pro Val Gly Gln Lys Lys Arg Lys Met Ser Leu Leu Phe Asp His Leu
 260 265 270

- 66 -

Glu Pro Met Glu Leu Ala Glu His Leu Thr Tyr Leu Glu Tyr Arg Ser
 275 280 285
 Phe Cys Lys Ile Leu Phe Gln Asp Tyr His Ser Phe Val Thr His Gly
 290 295 300
 Cys Thr Val Asp Asn Pro Val Leu Glu Arg Phe Ile Ser Leu Phe Asn
 305 310 315 320
 Ser Val Ser Gln Trp Val Gln Leu Met Ile Leu Ser Lys Pro Thr Ala
 325 330 335
 Pro Gln Arg Ala Leu Val Ile Thr His Phe Val His Val Ala Glu Lys
 340 345 350
 Leu Leu Gln Leu Gln Asn Phe Asn Thr Leu Met Ala Val Val Gly Gly
 355 360 365
 Leu Ser His Ser Ser Ile Ser Arg Leu Lys Glu Thr His Ser His Val
 370 375 380
 Ser Pro Glu Thr Ile Lys Leu Trp Glu Gly Leu Thr Glu Leu Val Thr
 385 390 395 400
 Ala Thr Gly Asn Tyr Gly Asn Tyr Arg Arg Arg Leu Ala Ala Cys Val
 405 410 415
 Gly Phe Arg Phe Pro Ile Leu Gly Val His Leu Lys Asp Leu Val Ala
 420 425 430
 Leu Gln Leu Ala Leu Pro Asp Trp Leu Asp Pro Ala Arg Thr Arg Leu
 435 440 445
 Asn Gly Ala Lys Met Lys Gln Leu Phe Ser Ile Leu Glu Glu Leu Ala
 450 455 460
 Met Val Thr Ser Leu Arg Pro Pro Val Gln Ala Asn Pro Asp Leu Leu
 465 470 475 480
 Ser Leu Leu Thr Val Ser Leu Asp Gln Tyr Gln Thr Glu Asp Glu Leu
 485 490 495
 Tyr Gln Leu Ser Leu Gln Arg Glu Pro Arg Ser Lys Ser Ser Pro Thr
 500 505 510
 Ser Pro Thr Ser Cys Thr Pro Pro Arg Pro Pro Val Leu Glu Glu
 515 520 525
 Trp Thr Ser Ala Ala Lys Pro Lys Leu Asp Gln Ala Leu Val Val Glu
 530 535 540
 His Ile Glu Lys Met Val Glu Ser Val Phe Arg Asn Phe Asp Val Asp
 545 550 555 560
 Gly Asp Gly His Ile Ser Gln Glu Glu Phe Gln Ile Ile Arg Gly Asn
 565 570 575
 Phe Pro Tyr Leu Ser Ala Phe Gly Asp Leu Asp Gln Asn Gln Asp Gly
 580 585 590
 Cys Ile Ser Arg Glu Glu Met Val Ser Tyr Phe Leu Arg Ser Ser Ser
 595 600 605
 Val Leu Gly Gly Arg Met Gly Phe Val His Asn Phe Gln Glu Ser Asn
 610 615 620
 Ser Leu Arg Pro Val Ala Cys Arg His Cys Lys Ala Leu Ile Leu Gly

- 67 -

625		630		635		640
Ile Tyr Lys Gln Gly	Leu Lys Cys Arg Ala	Cys Gly Val Asn Cys His				
	645		650		655	
Lys Gln Cys Lys Asp Arg Leu Ser Val	Glu Cys Arg Arg Arg Ala Gln					
	660	665		670		
Ser Val Ser Leu Glu Gly Ser Ala	Pro Ser Pro Ser Pro Met His Ser					
	675	680	685			
His His His Arg Ala Phe Ser Phe Ser Leu	Pro Arg Pro Gly Arg Arg					
	690	695	700			
Gly Ser Arg Pro Pro Glu Ile Arg Glu Glu	Glu Val Gln Thr Val Glu					
	705	710	715		720	
Asp Gly Val Phe Asp Ile His Leu						
	725					

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2309 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 254..2083

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGATTTCATT CCTCGCTCCC CACAGGTCCC TCTCCCCAAA ATATTCCCAT CTTGTCCTAG	60
CCCATCCCCC AGACTATCTC AAGGACCAGC TGTCCCCACG CCCCCGACCT CCACTAGGCC	120
TGTGCCACCC GCTGCCTGCA GGAAGACGCC CGGTCCCGGG CCGGGTTAGC CCCATGGGAA	180
CGGGGTTCGG TCCGAGCCCG GTGGGAGGCT CCCGGAGCGC AGCCTGGGCC CAGCCCACCC	240
CGCGCCGGCG GCC ATG GCA GGC ACC CTG GAC CTG GAC AAG GGC TGC ACG	289
Met Ala Gly Thr Leu Asp Leu Asp Lys Gly Cys Thr	
1 5 10	
GTG GAG GAG CTG CTC CGC GGG TGC ATC GAA GCC TTC GAT GAC TCC GGG	337
Val Glu Glu Leu Leu Arg Gly Cys Ile Glu Ala Phe Asp Asp Ser Gly	
15 20 25	
AAG GTG CGG GAC CCG CAG CTG GTG CGC ATG TTC CTC ATG ATG CAC CCC	385
Lys Val Arg Asp Pro Gln Leu Val Arg Met Phe Leu Met Met His Pro	
30 35 40	
TGG TAC ATC CCC TCC TCT CAG CTG GCG GCC AAG CTG CTC CAC ATC TAC	433
Trp Tyr Ile Pro Ser Ser Gln Leu Ala Ala Lys Leu Leu His Ile Tyr	
45 50 55 60	
CAA CAA TCC CGG AAG GAC AAC TCC AAT TCC CTG CAG GTG AAA ACG TGC	481
Gln Gln Ser Arg Lys Asp Asn Ser Asn Ser Leu Gln Val Lys Thr Cys	
65 70 75	
CAC CTG GTC AGG TAC TGG ATC TCC GCC TTC CCA GCG GAG TTT GAC TTG	529

- 68 -

His	Leu	Val	Arg	Tyr	Trp	Ile	Ser	Ala	Phe	Pro	Ala	Glu	Phe	Asp	Leu	
			80					85					90			
AAC	CCG	GAG	TTG	GCT	GAG	CAG	ATC	AAG	GAG	CTG	AAG	GCT	CTG	CTA	GAC	577
Asn	Pro	Glu	Leu	Ala	Glu	Gln	Ile	Lys	Glu	Leu	Lys	Ala	Leu	Leu	Asp	
		95					100				105					
CAA	GAA	GGG	AAC	CGA	CGG	CAC	AGC	AGC	CTA	ATC	GAC	ATA	GAC	AGC	GTC	625
Gln	Gly	Gly	Asn	Arg	Arg	His	Ser	Ser	Leu	Ile	Asp	Ile	Asp	Ser	Val	
	110					115					120					
CCT	ACC	TAC	AAG	TGG	AAG	CGG	CAG	GTG	ACT	CAG	CGG	AAC	CCT	GTG	GGA	673
Pro	Thr	Tyr	Lys	Trp	Lys	Arg	Gln	Val	Thr	Gln	Arg	Asn	Pro	Val	Gly	
	125				130					135					140	
CAG	AAA	AAG	CGC	AAG	ATG	TCC	CTG	TTG	TTT	GAC	CAC	CTG	GAG	CCC	ATG	721
Gln	Lys	Lys	Arg	Lys	Met	Ser	Leu	Leu	Phe	Asp	His	Leu	Glu	Pro	Met	
				145					150					155		
GAG	CTG	GCG	GAG	CAT	CTC	ACC	TAC	TTG	GAG	TAT	CGC	TCC	TTC	TGC	AAG	769
Glu	Leu	Ala	Glu	His	Leu	Thr	Tyr	Leu	Glu	Tyr	Arg	Ser	Phe	Cys	Lys	
			160					165					170			
ATC	CTG	TTT	CAG	GAC	TAT	CAC	AGT	TTC	GTG	ACT	CAT	GGC	TGC	ACT	GTG	817
Ile	Leu	Phe	Gln	Asp	Tyr	His	Ser	Phe	Val	Thr	His	Gly	Cys	Thr	Val	
		175					180					185				
GAC	AAC	CCC	GTC	CTG	GAG	CGG	TTC	ATC	TCC	CTC	TTC	AAC	AGC	GTC	TCA	865
Asp	Asn	Pro	Val	Leu	Glu	Arg	Phe	Ile	Ser	Leu	Phe	Asn	Ser	Val	Ser	
		190				195					200					
CAG	TGG	GTG	CAG	CTC	ATG	ATC	CTC	AGC	AAA	CCC	ACA	GCC	CCG	CAG	CGG	913
Gln	Trp	Val	Gln	Leu	Met	Ile	Leu	Ser	Lys	Pro	Thr	Ala	Pro	Gln	Arg	
	205				210					215					220	
GCC	CTG	GTC	ATC	ACA	CAC	TTT	GTC	CAC	GTG	GCG	GAG	AAG	CTG	CTA	CAG	961
Ala	Leu	Val	Ile	Thr	His	Phe	Val	His	Val	Ala	Glu	Lys	Leu	Leu	Gln	
				225					230					235		
CTG	CAG	AAC	TTC	AAC	ACG	CTG	ATG	GCA	GTG	GTC	GGG	GGC	CTG	AGC	CAC	1009
Leu	Gln	Asn	Phe	Asn	Thr	Leu	Met	Ala	Val	Val	Gly	Gly	Leu	Ser	His	
			240					245					250			
AGC	TCC	ATC	TCC	CGC	CTC	AAG	GAG	ACC	CAC	AGC	CAC	GTT	AGC	CCT	GAG	1057
Ser	Ser	Ile	Ser	Arg	Leu	Lys	Glu	Thr	His	Ser	His	Val	Ser	Pro	Glu	
		255					260					265				
ACC	ATC	AAG	CTC	TGG	GAG	GGT	CTC	ACG	GAA	CTA	GTG	ACG	GCG	ACA	GGC	1105
Thr	Ile	Lys	Leu	Trp	Glu	Gly	Leu	Thr	Glu	Leu	Val	Thr	Ala	Thr	Gly	
	270					275					280					
AAC	TAT	GGC	AAC	TAC	CGG	CGT	CGG	CTG	GCA	GCC	TGT	GTG	GGC	TTC	CGC	1153
Asn	Tyr	Gly	Asn	Tyr	Arg	Arg	Arg	Leu	Ala	Ala	Cys	Val	Gly	Phe	Arg	
	285				290					295					300	
TTC	CCG	ATC	CTG	GGT	GTG	CAC	CTC	AAG	GAC	CTG	GTG	GCC	CTG	CAG	CTG	1201
Phe	Pro	Ile	Leu	Gly	Val	His	Leu	Lys	Asp	Leu	Val	Ala	Leu	Gln	Leu	
				305					310					315		
GCA	CTG	CCT	GAC	TGG	CTG	GAC	CCA	GCC	CGG	ACC	CGG	CTC	AAC	GGG	GCC	1249
Ala	Leu	Pro	Asp	Trp	Leu	Asp	Pro	Ala	Arg	Thr	Arg	Leu	Asn	Gly	Ala	
			320					325					330			
AAG	ATG	AAG	CAG	CTC	TTT	AGC	ATC	CTG	GAG	GAG	CTG	GCC	ATG	GTG	ACC	1297
Lys	Met	Lys	Gln	Leu	Phe	Ser	Ile	Leu	Glu	Glu	Leu	Ala	Met	Val	Thr	
		335					340					345				

AGC Ser 350	CTG Leu	CGG Arg	CCA Pro	CCA Pro	GTA Val	CAG Gln 355	GCC Ala	AAC Asn	CCC Pro	GAC Asp 360	CTG Leu	CTG Leu	AGC Ser	CTG Leu	CTC Leu	1345
ACG Thr 365	GTG Val	TCT Ser	CTG Leu	GAT Asp	CAG Gln 370	TAT Tyr	CAG Gln	ACG Thr	GAG Glu	GAT Asp 375	GAG Glu	CTG Leu	TAC Tyr	CAG Gln	CTG Leu 380	1393
TCC Ser	CTG Leu	CAG Gln	CGG Arg	GAG Glu 385	CCG Pro	CGC Arg	TCC Ser	AAG Lys	TCC Ser 390	TCG Ser	CCA Pro	ACC Thr	AGC Ser	CCC Pro 395	ACG Thr	1441
AGT Ser	TGC Cys	ACC Thr 400	CCA Pro	CCA Pro	CCC Pro	CGG Arg	CCC Pro	CCG Pro 405	GTA Val	CTG Leu	GAG Glu	GAG Glu	TGG Trp 410	ACC Thr	TCG Ser	1489
GCT Ala	GCC Ala	AAA Lys 415	CCC Pro	AAG Lys	CTG Leu	GAT Asp	CAG Gln 420	GCC Ala	CTC Leu	GTG Val	GTG Val	GAG Glu 425	CAC His	ATC Ile	GAG Glu	1537
AAG Lys 430	ATG Met	GTG Val	GAG Glu	TCT Ser	GTG Val	TTC Phe 435	CGG Arg	AAC Asn	TTT Phe	GAC Asp 440	GTC Val	GAT Asp	GGG Gly	GAT Asp	GGC Gly	1585
CAC His 445	ATC Ile	TCA Ser	CAG Gln	GAA Glu 450	GAA Glu	TTC Phe	CAG Gln	ATC Ile	ATC Ile	CGT Arg 455	GGG Gly	AAC Asn	TTC Phe	CCT Pro	TAC Tyr 460	1633
CTC Leu	AGC Ser	GCC Ala	TTT Phe	GGG Gly 465	GAC Asp	CTC Leu	GAC Asp	CAG Gln	AAC Asn 470	CAG Gln	GAT Asp	GGC Gly	TGC Cys	ATC Ile 475	AGC Ser	1681
AGG Arg	GAG Glu	GAG Glu	ATG Met 480	GTT Val	TCC Ser	TAT Tyr	TTC Phe	CTG Leu 485	CGC Arg	TCC Ser	AGC Ser	TCT Ser	GTG Val 490	TTG Leu	GGG Gly	1729
GGG Gly	CGC Arg	ATG Met 495	GGC Gly	TTC Phe	GTA Val	CAC His	AAC Asn 500	TTC Phe	CAG Gln	GAG Glu	AGC Ser	AAC Asn 505	TCC Ser	TTG Leu	CGC Arg	1777
CCC Pro 510	GTC Val	GCC Ala	TGC Cys	CGC Arg	CAC His	TGC Cys 515	AAA Lys	GCC Ala	CTG Leu	ATC Ile	CTG Leu 520	GGC Gly	ATC Ile	TAC Tyr	AAG Lys	1825
CAG Gln 525	GGC Gly	CTC Leu	AAA Lys	TGC Cys	CGA Ala 530	GCC Ala	TGT Cys	GGA Gly	GTG Val	AAC Asn 535	TGC Cys	CAC His	AAG Lys	CAG Gln	TGC Cys 540	1873
AAG Lys	GAT Asp	CGC Arg	CTG Leu	TCA Ser 545	GTT Val	GAG Glu	TGT Cys	CGG Arg	CGC Arg	AGG Arg 550	GCC Ala	CAG Gln	AGT Ser	GTG Val 555	AGC Ser	1921
CTG Leu	GAG Glu	GGG Gly	TCT Ser 560	GCA Ala	CCC Pro	TCA Ser	CCC Pro	TCA Ser 565	CCC Pro	ATG Met	CAC His	AGC Ser	CAC His 570	CAT His	CAC His	1969
CGC Arg	GCC Ala	TTC Phe 575	AGC Ser	TTC Phe	TCT Ser	CTG Leu	CCC Pro 580	CGC Arg	CCT Pro	GGC Gly	AGG Arg	CGA Arg 585	GGC Gly	TCC Ser	AGG Arg	2017
CCT Pro 590	CCA Pro	GAG Glu	ATC Ile	CGT Arg	GAG Glu	GAG Glu 595	GAG Glu	GTA Val	CAG Gln	ACG Thr	GTG Val 600	GAG Glu	GAT Asp	GGG Gly	GTG Val	2065
TTT Phe 605	GAC Asp	ATC Ile	CAC His	TTG Leu	TAATAGATGC TGTGGTTGGA TCAAGGACTC ATTCTGCCT											2120

- 70 -

TGGAGAAAAT ACTTCAACCA GAGCAGGGAG CCTGGGGGTG TCGGGGCAGG AGGCTGGGGA	2180
TGGGGGTGGG ATATGAGGGT GGCATGCAGC TGAGGGCAGG GCCAGGGCTG GTGTCCCTAA	2240
GGTTGTACAG ACTCTTGTGA ATATTTGTAT TTTCCAGATG GAATAAAAAG GCCCGTGTA	2300
TTAACCTTC	2309

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 609 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met	Ala	Gly	Thr	Leu	Asp	Leu	Asp	Lys	Gly	Cys	Thr	Val	Glu	Glu	Leu	1	5	10	15
Leu	Arg	Gly	Cys	Ile	Glu	Ala	Phe	Asp	Asp	Ser	Gly	Lys	Val	Arg	Asp	20	25	30	
Pro	Gln	Leu	Val	Arg	Met	Phe	Leu	Met	Met	His	Pro	Trp	Tyr	Ile	Pro	35	40	45	
Ser	Ser	Gln	Leu	Ala	Ala	Lys	Leu	Leu	His	Ile	Tyr	Gln	Gln	Ser	Arg	50	55	60	
Lys	Asp	Asn	Ser	Asn	Ser	Leu	Gln	Val	Lys	Thr	Cys	His	Leu	Val	Arg	65	70	75	80
Tyr	Trp	Ile	Ser	Ala	Phe	Pro	Ala	Glu	Phe	Asp	Leu	Asn	Pro	Glu	Leu	85	90	95	
Ala	Glu	Gln	Ile	Lys	Glu	Leu	Lys	Ala	Leu	Leu	Asp	Gln	Glu	Gly	Asn	100	105	110	
Arg	Arg	His	Ser	Ser	Leu	Ile	Asp	Ile	Asp	Ser	Val	Pro	Thr	Tyr	Lys	115	120	125	
Trp	Lys	Arg	Gln	Val	Thr	Gln	Arg	Asn	Pro	Val	Gly	Gln	Lys	Lys	Arg	130	135	140	
Lys	Met	Ser	Leu	Leu	Phe	Asp	His	Leu	Glu	Pro	Met	Glu	Leu	Ala	Glu	145	150	155	160
His	Leu	Thr	Tyr	Leu	Glu	Tyr	Arg	Ser	Phe	Cys	Lys	Ile	Leu	Phe	Gln	165	170	175	
Asp	Tyr	His	Ser	Phe	Val	Thr	His	Gly	Cys	Thr	Val	Asp	Asn	Pro	Val	180	185	190	
Leu	Glu	Arg	Phe	Ile	Ser	Leu	Phe	Asn	Ser	Val	Ser	Gln	Trp	Val	Gln	195	200	205	
Leu	Met	Ile	Leu	Ser	Lys	Pro	Thr	Ala	Pro	Gln	Arg	Ala	Leu	Val	Ile	210	215	220	
Thr	His	Phe	Val	His	Val	Ala	Glu	Lys	Leu	Leu	Gln	Leu	Gln	Asn	Phe	225	230	235	240
Asn	Thr	Leu	Met	Ala	Val	Val	Gly	Gly	Leu	Ser	His	Ser	Ser	Ile	Ser	245	250	255	

- 71 -

Arg Leu Lys Glu Thr His Ser His Val Ser Pro Glu Thr Ile Lys Leu
 260 265 270
 Trp Glu Gly Leu Thr Glu Leu Val Thr Ala Thr Gly Asn Tyr Gly Asn
 275 280 285
 Tyr Arg Arg Arg Leu Ala Ala Cys Val Gly Phe Arg Phe Pro Ile Leu
 290 295 300
 Gly Val His Leu Lys Asp Leu Val Ala Leu Gln Leu Ala Leu Pro Asp
 305 310 315 320
 Trp Leu Asp Pro Ala Arg Thr Arg Leu Asn Gly Ala Lys Met Lys Gln
 325 330 335
 Leu Phe Ser Ile Leu Glu Glu Leu Ala Met Val Thr Ser Leu Arg Pro
 340 345 350
 Pro Val Gln Ala Asn Pro Asp Leu Leu Ser Leu Leu Thr Val Ser Leu
 355 360 365
 Asp Gln Tyr Gln Thr Glu Asp Glu Leu Tyr Gln Leu Ser Leu Gln Arg
 370 375 380
 Glu Pro Arg Ser Lys Ser Ser Pro Thr Ser Pro Thr Ser Cys Thr Pro
 385 390 395 400
 Pro Pro Arg Pro Pro Val Leu Glu Glu Trp Thr Ser Ala Ala Lys Pro
 405 410 415
 Lys Leu Asp Gln Ala Leu Val Val Glu His Ile Glu Lys Met Val Glu
 420 425 430
 Ser Val Phe Arg Asn Phe Asp Val Asp Gly Asp Gly His Ile Ser Gln
 435 440 445
 Glu Glu Phe Gln Ile Ile Arg Gly Asn Phe Pro Tyr Leu Ser Ala Phe
 450 455 460
 Gly Asp Leu Asp Gln Asn Gln Asp Gly Cys Ile Ser Arg Glu Glu Met
 465 470 475 480
 Val Ser Tyr Phe Leu Arg Ser Ser Ser Val Leu Gly Gly Arg Met Gly
 485 490 495
 Phe Val His Asn Phe Gln Glu Ser Asn Ser Leu Arg Pro Val Ala Cys
 500 505 510
 Arg His Cys Lys Ala Leu Ile Leu Gly Ile Tyr Lys Gln Gly Leu Lys
 515 520 525
 Cys Arg Ala Cys Gly Val Asn Cys His Lys Gln Cys Lys Asp Arg Leu
 530 535 540
 Ser Val Glu Cys Arg Arg Arg Ala Gln Ser Val Ser Leu Glu Gly Ser
 545 550 555 560
 Ala Pro Ser Pro Ser Pro Met His Ser His His His Arg Ala Phe Ser
 565 570 575
 Phe Ser Leu Pro Arg Pro Gly Arg Arg Gly Ser Arg Pro Pro Glu Ile
 580 585 590
 Arg Glu Glu Glu Val Gln Thr Val Glu Asp Gly Val Phe Asp Ile His
 595 600 605
 Leu

- 72 -

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 832 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

- (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 11..733

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCCCGCCGCC	ATG	CCG	CCC	TTA	CTG	CCC	CTG	CGC	CTG	TGC	CGG	CTG	TGG	49
	Met	Pro	Pro	Leu	Leu	Pro	Leu	Arg	Leu	Cys	Arg	Leu	Trp	
	1				5					10				
CCC	CGC	AAC	CCT	CCC	TCC	CGG	CTC	CTC	GGA	GCG	GCC	GCC	GGG	97
Pro	Arg	Asn	Pro	Pro	Ser	Arg	Leu	Leu	Gly	Ala	Ala	Ala	Gly	
	15				20					25			Gln	
TCC	AGA	CCC	AGT	ACT	TAT	TAT	GAA	CTG	TTG	GGG	GTG	CAT	CCT	145
Ser	Arg	Pro	Ser	Thr	Tyr	Tyr	Glu	Leu	Leu	Gly	Val	His	Pro	
	30				35					40			Gly	45
AGC	ACT	GAG	GAA	GTT	AAA	CGA	GCT	TTC	TTC	TCC	AAG	TCC	AAA	193
Ser	Thr	Glu	Glu	Val	Lys	Arg	Ala	Phe	Phe	Ser	Lys	Ser	Lys	
				50					55				Glu	60
CAC	CCA	GAC	CGG	GAC	CCT	GGG	AAC	CCA	AGC	CTG	CAC	AGC	CGC	241
His	Pro	Asp	Arg	Asp	Pro	Gly	Asn	Pro	Ser	Leu	His	Ser	Arg	
			65				70						Phe	75
GAG	CTG	AGC	GAG	GCA	TAC	CGT	GTG	CTC	AGC	CGT	GAG	CAG	AGC	289
Glu	Leu	Ser	Glu	Ala	Tyr	Arg	Val	Leu	Ser	Arg	Glu	Gln	Ser	
	80						85					90	Arg	
AGC	TAT	GAT	GAC	CAG	CTC	CGC	TCA	GGT	AGT	CCC	CCA	AAG	TCT	337
Ser	Tyr	Asp	Asp	Gln	Leu	Arg	Ser	Gly	Ser	Pro	Pro	Lys	Ser	
	95				100					105			Pro	
ACC	ACA	GTC	CAT	GAC	AAG	TCT	GCC	CAC	CAA	ACA	CAC	AGC	TCC	385
Thr	Thr	Val	His	Asp	Lys	Ser	Ala	His	Gln	Thr	His	Ser	Ser	
	110				115					120			Trp	125
CCC	CCC	AAC	GCA	CAG	TAC	TGG	TCC	CAG	TTT	CAC	AGC	GTG	AGG	433
Pro	Pro	Asn	Ala	Gln	Tyr	Trp	Ser	Gln	Phe	His	Ser	Val	Arg	
				130					135				Pro	140
GGG	CCC	CAG	TTG	AGG	CAG	CAG	CAA	CAC	AAA	CAA	AAC	AAA	CAA	481
Gly	Pro	Gln	Leu	Arg	Gln	Gln	Gln	His	Lys	Gln	Asn	Lys	Gln	
			145					150				155	Val	
GGG	TAC	TGC	CTC	CTC	CTC	ATG	CTG	GCG	GGC	ATG	GGC	CTG	CAC	529
Gly	Tyr	Cys	Leu	Leu	Leu	Met	Leu	Ala	Gly	Met	Gly	Leu	His	
		160					165					170	Tyr	
GCC	TTC	AGG	AAG	GTG	AAG	CAG	ATG	CAC	CTT	AAC	TTC	ATG	GAT	577
Ala	Phe	Arg	Lys	Val	Lys	Gln	Met	His	Leu	Asn	Phe	Met	Asp	
						180					185		Glu	

- 73 -

GAT CGG ATC ATC ACA GCC TTC TAC AAC GAA GCC CGG GCA CGG GCC AGG	625
Asp Arg Ile Ile Thr Ala Phe Tyr Asn Glu Ala Arg Ala Arg Ala Arg	
190 195 200 205	
GCC AAC AGA GGC ATC CTT CAG CAG GAG CGA CAA CGG CTA GGG CAG CGG	673
Ala Asn Arg Gly Ile Leu Gln Gln Glu Arg Gln Arg Leu Gly Gln Arg	
210 215 220	
CAG CCG CCA CCA TCC GAG CCA ACC CAA GGC CCC GAG ATC GTG CCC CGG	721
Gln Pro Pro Pro Ser Glu Pro Thr Gln Gly Pro Glu Ile Val Pro Arg	
225 230 235	
GGC GCC GGC CCC TGA GGGGCTC ACCTGGATGG GGCCTGCAGT GCGTTCCCGC	773
Gly Ala Gly Pro *	
240	
TTTGCTTCCT TCCCTGGACG GCCCGCTCCC CGAAACGCGC GCAATAAAGT GATTTCGCAG	832

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 241 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met	Pro	Pro	Leu	Leu	Pro	Leu	Arg	Leu	Cys	Arg	Leu	Trp	Pro	Arg	Asn
1				5					10					15	
Pro	Pro	Ser	Arg	Leu	Leu	Gly	Ala	Ala	Ala	Gly	Gln	Arg	Ser	Arg	Pro
			20					25					30		
Ser	Thr	Tyr	Tyr	Glu	Leu	Leu	Gly	Val	His	Pro	Gly	Ala	Ser	Thr	Glu
		35					40					45			
Glu	Val	Lys	Arg	Ala	Phe	Phe	Ser	Lys	Ser	Lys	Glu	Leu	His	Pro	Asp
	50					55					60				
Arg	Asp	Pro	Gly	Asn	Pro	Ser	Leu	His	Ser	Arg	Phe	Val	Glu	Leu	Ser
	65				70					75					80
Glu	Ala	Tyr	Arg	Val	Leu	Ser	Arg	Glu	Gln	Ser	Arg	Arg	Ser	Tyr	Asp
				85					90					95	
Asp	Gln	Leu	Arg	Ser	Gly	Ser	Pro	Pro	Lys	Ser	Pro	Arg	Thr	Thr	Val
			100					105					110		
His	Asp	Lys	Ser	Ala	His	Gln	Thr	His	Ser	Ser	Trp	Thr	Pro	Pro	Asn
		115					120					125			
Ala	Gln	Tyr	Trp	Ser	Gln	Phe	His	Ser	Val	Arg	Pro	Gln	Gly	Pro	Gln
	130					135					140				
Leu	Arg	Gln	Gln	Gln	His	Lys	Gln	Asn	Lys	Gln	Val	Leu	Gly	Tyr	Cys
	145				150					155					160
Leu	Leu	Leu	Met	Leu	Ala	Gly	Met	Gly	Leu	His	Tyr	Ile	Ala	Phe	Arg
			165					170						175	
Lys	Val	Lys	Gln	Met	His	Leu	Asn	Phe	Met	Asp	Glu	Lys	Asp	Arg	Ile
			180					185					190		
Ile	Thr	Ala	Phe	Tyr	Asn	Glu	Ala	Arg	Ala	Arg	Ala	Arg	Ala	Asn	Arg

- 74 -

195		200		205
Gly Ile Leu Gln Gln Glu Arg Gln Arg Leu Gly Gln Arg Gln Pro Pro				
210		215		220
Pro Ser Glu Pro Thr Gln Gly Pro Glu Ile Val Pro Arg Gly Ala Gly				
225		230		240
Pro				

SEQ ID Nos: 10-18 25-36

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 300 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 170..300

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGATTTTCATT CCTCGCTCCC CACAGGTCCC TCTCCCCAAA ATATTCCCAT CTTGTCCTAG	60
CCCATCCCCC AGACTATCTC AAGGACCAGC TGTCCCCACG CCCCCGACCT CCAC TAGGCC	120
TGTGCCACCC GCTGCCTGCA GGAAGACGCC CGGTCCC GGG CCGGGTTAG CCC CAT	175
	Pro His 1
GGG AAC GGG GTT CGG TCC GAG CCC GGT GGG AGG CTC CCG GAG CGC AGC	223
Gly Asn Gly Val Arg Ser Glu Pro Gly Gly Arg Leu Pro Glu Arg Ser	
5 10 15	
CTG GGC CCA GCC CAC CCC GCG CCG GCG GCC ATG GCA GGC ACC CTG GAC	271
Leu Gly Pro Ala His Pro Ala Pro Ala Ala Met Ala Gly Thr Leu Asp	
20 25 30	
CTG GAC AAG GGC TGC ACG GTG GAG GAG CT	300
Leu Asp Lys Gly Cys Thr Val Glu Glu Leu	
35 40	

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 44 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

- 75 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Pro His Gly Asn Gly Val Arg Ser Glu Pro Gly Gly Arg Leu Pro Glu
 1 5 10 15
 Arg Ser Leu Gly Pro Ala His Pro Ala Pro Ala Ala Met Ala Gly Thr
 20 25 30
 Leu Asp Leu Asp Lys Gly Cys Thr Val Glu Glu Leu
 35 40

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGATCCCC TGGTC

15

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 13 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asp Val Asp Glu Glu Asp Glu Val Glu Asp Ile Glu Phe
 1 5 10

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 13 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Asp Val Asp Gly Asp Gly His Ile Ser Gln Glu Glu Phe
 1 5 10

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 13 amino acids

- 76 -

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asp His Asp Arg Asp Gly Phe Ile Ser Gln Glu Glu Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asp Gln Asn Gln Asp Gly Cys Ile Ser Arg Glu Glu Met
1 5 10

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Asp Val Asp Met Asp Gly Gln Ile Ser Lys Asp Glu Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

His Phe Val His Val Ala Glu Lys Leu Leu Gln Leu Gln Asn Phe Asn
1 5 10 15
Thr Leu Met Ala Val Val Gly Gly Leu Ser His Ser Ser Ile Ser Arg
20 25 30

- 77 -

Leu Lys Glu Thr His
35

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 37 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Lys Phe Val His Val Ala Lys His Leu Arg Lys Ile Asn Asn Phe Asn
1 5 10 15
 Thr Leu Met Ser Val Val Gly Gly Ile Thr His Ser Ser Val Ala Arg
20 25 30
 Leu Ala Lys Thr Tyr
35

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

His Asn Phe Gln Glu Ser Asn Ser Leu Arg Pro Val Ala Cys Arg His
1 5 10 15
 Cys Lys Ala Leu Ile Leu Gly Ile Tyr Lys Gln Gly Leu Lys Cys Arg
20 25 30
 Ala Cys Gly Val Asn Cys His Lys Gln Cys Lys Asp Arg Leu Ser Val
35 40 45
 Glu Cys
50

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 50 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

His Asn Phe His Glu Thr Thr Phe Leu Thr Pro Thr Thr Cys Asn His

- 78 -

1	5	10	15
Cys Asn Lys	Leu Leu Trp Gly Ile	Leu Arg Gln Gly Phe	Lys Cys Lys
	20	25	30
Asp Cys Gly	Leu Ala Val His Ser	Cys Cys Lys Ser	Asn Ala Val Ala
	35	40	45
Glu Cys			
50			

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GGGATCCCC TGGTC

15

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GAATTCGGCA CGAGCCGACG G

21

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 78 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ATGGAGCAGA AGCTGATCTC CGAGGAGGAC CTGCCCGGGG CAGCTGGATC CGCAGCCCAC
 CCCGCGCCGG CGGCCATG

60

78

(2) INFORMATION FOR SEQ ID NO:22:

- 79 -

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 26 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

Met Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Pro Gly Ala Ala Gly
 1           5           10           15
Ser Ala Ala His Pro Ala Pro Ala Ala Met
          20           25

```

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GGATCCGCAG CCCACCCCGC GCCGGCGGCC ATG

33

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 11 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```

Gly Ser Ala Ala His Pro Ala Pro Ala Ala Met
          5           10

```

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

- 80 -

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:
GGACAAAGTG TGTGATGAAC C 21
- (2) INFORMATION FOR SEQ ID NO:26:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:
CTCATCCTCC GTCTGATACT G 21
- (2) INFORMATION FOR SEQ ID NO:27:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
GTAGATGTGG ATCAGCTTGG 20
- (2) INFORMATION FOR SEQ ID NO:28:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:
AGGTGGAGAA TGGTCAAGG 19
- (2) INFORMATION FOR SEQ ID NO:29:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:
GTCATAGTCT GTCTCCTACT 20

- 81 -

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ACATAGACAG CGTGCCTACC

20

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TACAACCTTA GGGACACCAG

20

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TGCTGAGCCT GCTCACGGTG

20

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CAAGTGAACA GCACGTCC

18

(2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:

- 82 -

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GACTATCTCA AGGACCAGCT G

21

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GGTTCGGTCC GAGCCCGG

18

(2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GGAGCGATAC TCCAAGTAGG T

21

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AGCGGGCCAG GCCCCTTC

18

(2) INFORMATION FOR SEQ ID NO:38:

- 83 -

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CATCCTGGTC CAATGCGCTC

20

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GCACTGAGGA AGTTAAACGA GC

22

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GCTCGTTTAA CTCCTCAGT GC

22

(2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GCTCAGCTCC ACAAAGCGGC T

21

(2) INFORMATION FOR SEQ ID NO:42:

- 84 -

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

ACCAGCTCCG CTCAGGTAG

19

(2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TCCAGGAGCT GTGTGTTTGG

20

(2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CCAGTTTCAC AGCGTGAGG

19

(2) INFORMATION FOR SEQ ID NO:45:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 19 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGCATGAGG AGGAGGCAG

19

CLAIMS:

1. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding an amino acid sequence having homology to a regulator of gene expression or a derivative of said gene regulator.
2. An isolated nucleic acid molecule according to claim 1 wherein the regulator comprises a zinc finger domain of an $(\text{HC}_3)_2$ type.
3. An isolated nucleic acid molecule according to claim 2 wherein the sequence of nucleotides or complementary sequence of nucleotides is selected from:
 - (i) a nucleotide sequence set forth in SEQ ID NO:2;
 - (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:3;
 - (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
 - (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the nucleotide sequence set forth in (i), (ii) or (iii).
4. An isolated nucleic acid molecule according to claim 1 wherein said gene regulator is a guanine nucleotide exchange factor (GEF) or a derivative thereof.
5. An isolated nucleic acid molecule according to claim 4 wherein the sequence of nucleotides is selected from:
 - (i) a nucleotide sequence set forth in SEQ ID NO:4 or 6;
 - (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:5 or 7;
 - (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
 - (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the

nucleotide sequence set forth in (i), (ii) or (iii).

6. An isolated nucleic acid molecule according to claim 1, wherein said gene regulator is a heat shock protein or is a heat shock binding protein or a derivative thereof.

7. An isolated nucleic acid molecule according to claim 6, wherein the sequence of nucleotides is selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:8;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:9;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the nucleotide sequence set forth in (i), (ii) or (iii).

8. A genetic construct comprising a vector portion and a gene portion comprising a regulator of gene expression or a derivative thereof .

9. A genetic construct according to claim 8 wherein the gene portion comprises a zinc finger domain of $(\text{HC}_3)_2$ type.

10. A genetic construct according to claim 9 wherein the gene portion comprises a nucleotide sequence selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:2;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:3;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the nucleotide sequence set forth in (i), (ii) or (iii).

11. A genetic construct according to claim 8 wherein said gene portion is a nucleotide exchange factor (GEF) or derivative thereof.

12. A genetic construct according to claim 11 wherein the gene portion comprises a nucleotide sequence selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:4 or 6;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:5 or 7;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the nucleotide sequence set forth in (i), (ii) or (iii).

13. A genetic construct according to claim 8 wherein the gene portion is a heat shock protein or a derivative thereof or a heat shock binding protein or derivative thereof.

14. A genetic construct according to claim 13 wherein the gene portion comprises a nucleotide sequence selected from:

- (i) a nucleotide sequence set forth in SEQ ID NO:8;
- (ii) a nucleotide sequence encoding an amino acid sequence set forth in SEQ ID NO:9;
- (iii) a nucleotide sequence having at least about 40% similarity to the nucleotide sequence of (i) or (ii); and
- (iv) a nucleotide sequence capable of hybridising under low stringency conditions to the nucleotide sequence set forth in (i), (ii) or (iii).

15. A nucleic acid molecule encoding a gene regulator having the identifying characteristics of a molecule selected from MCG4, MCG7 and MCG18 having respective amino acid sequences of SEQ ID NO:3, SEQ ID NO: 5 or 7 and SEQ ID NO:9.

16. A method of detecting a condition caused or facilitated by an aberration in *mcg4*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg4* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

17. A method of detecting a condition caused or facilitated by an aberration in *mcg4*, said method comprising screening for a single or multiple amino acid substitution, deletion and/or addition to MCG4 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

18. A method for detecting MCG4 or a derivative thereof in a biological sample said method comprising contacting said biological sample with an antibody specific for MCG4 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG4 complex to form, and then detecting said complex.

19. A method of detecting a condition caused or facilitated by an aberration in *mcg7*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg7* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

20. A method of detecting a condition caused or facilitated by an aberration in *mcg7*, said method comprising screening for a single or multiple amino acid substitution, deletion and/or addition to MCG7 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

21. A method for detecting MCG7 or a derivative thereof in a biological sample said method comprising contacting said biological sample with an antibody specific for MCG7 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG7 complex to form, and then detecting said complex.

22. A method of detecting a condition caused or facilitated by an aberration in *mcg18*, said method comprising determining the presence of a single or multiple nucleotide substitution, deletion and/or addition or other aberration to one or both alleles of said *mcg18* wherein the presence of such a nucleotide substitution, deletion and/or addition or other aberration may be indicative of said condition or a propensity to develop said condition.

23. A method of detecting a condition caused or facilitated by an aberration in *mcg18*, said method comprising screening for a single or multiple amino acid substitution, deletion and/or addition to MCG18 wherein the presence of such a mutation is indicative of or a propensity to develop said condition.

24. A method for detecting MCG18 or a derivative thereof in a biological sample said method comprising contacting said biological sample with an antibody specific for MCG18 or its derivatives or homologues for a time and under conditions sufficient for an antibody-MCG18 complex to form, and then detecting said complex.

FIGURE 1

TCAGTAAACA CAGAGACTGG GGATCGATC ATG GGG CTT TGT AAG TGC CCC AAG	53
Met Gly Leu Cys Lys Cys Pro Lys	
1 5	
AGA AAG GTG ACC AAC CTG TTC TGC TTC GAA CAT CGG GTC AAC GTC TGC	101
Arg Lys Val Thr Asn Leu Phe Cys Phe Glu His Arg Val Asn Val Cys	
10 15 20	
GAG CAC TGC CTG GTA GCC AAT CAC GCC AAG TGC ATC GTC CAG TCC TAC	149
Glu His Cys Leu Val Ala Asn His Ala Lys Cys Ile Val Gln Ser Tyr	
25 30 35 40	
CTG CAA TGG CTC CAA GAT AGC GAC TAC AAC CCC AAT TGC CGC CTG TGC	197
Leu Gln Trp Leu Gln Asp Ser Asp Tyr Asn Pro Asn Cys Arg Leu Cys	
45 50 55	
AAC ATA CCC CTG GCC AGC CGA GAG ACG ACC CGC CTT GTC TGC TAT GAT	245
Asn Ile Pro Leu Ala Ser Arg Glu Thr Thr Arg Leu Val Cys Tyr Asp	
60 65 70	
CTC TTT CAC TGG GCC TGC CTC AAT GAA CGT GCT GCC CAG CTA CCC CGA	293
Leu Phe His Trp Ala Cys Leu Asn Glu Arg Ala Ala Gln Leu Pro Arg	
75 80 85	
AAC ACG GCA CCT GCC GGC TAT CAG TGC CCC AGC TGC AAT GGC CCC ATC	341
Asn Thr Ala Pro Ala Gly Tyr Gln Cys Pro Ser Cys Asn Gly Pro Ile	
90 95 100	
TTC CCC CCA ACC AAC CTG GCT GGC CCC GTG GCC TCC GCA CTG AGA GAG	389
Phe Pro Pro Thr Asn Leu Ala Gly Pro Val Ala Ser Ala Leu Arg Glu	
105 110 115 120	
AAG CTG GCC ACA GTC AAC TGG GCC CGG GCA GGA CTG GGC CTC CCT CTG	437
Lys Leu Ala Thr Val Asn Trp Ala Arg Ala Gly Leu Gly Leu Pro Leu	
125 130 135	
ATC GAT GAG GTG GTG AGC CCA GAG CCC GAG CCC CTC AAC ACG TCT GAC	485
Ile Asp Glu Val Val Ser Pro Glu Pro Glu Pro Leu Asn Thr Ser Asp	
140 145 150	
TTC TCT GAC TGG TCT AGT TTT AAT GCC AGC AGT ACC CCT GGA CCA GAG	533
Phe Ser Asp Trp Ser Ser Phe Asn Ala Ser Ser Thr Pro Gly Pro Glu	
155 160 165	
GAG GTA GAC AGC GCC TCT GCT GCC CCA GCC TTC TAC AGC CGA GCC CCC	581
Glu Val Asp Ser Ala Ser Ala Ala Pro Ala Phe Tyr Ser Arg Ala Pro	
170 175 180	
CGG CCC CCA GCT TCC CCA GGC CGG CCC GAG CAG CAC ACA GTG ATC CAC	629
Arg Pro Pro Ala Ser Pro Gly Arg Pro Glu Gln His Thr Val Ile His	
185 190 195 200	
ATG GGC AAT CCT GAG CCC TTG ACT CAC GCC CCT AGG AAG GTG TAT GAT	677
Met Gly Asn Pro Glu Pro Leu Thr His Ala Pro Arg Lys Val Tyr Asp	
205 210 215	

ACG CGG GAT GAT GAC CGG ACA CCA GGC CTC CAT GGA GAC T. GAC GAT	745
Thr Arg Asp Asp Asp Arg Thr Pro Gly Leu His Gly Asp Cys Asp Asp	
220 225 230	
GAC AAG TAC CGA CGT CGG CCG GCC TTG GGT TGG CTG GCC CGG CTG CTA	773
Asp Lys Tyr Arg Arg Arg Pro Ala Leu Gly Trp Leu Ala Arg Leu Leu	
235 240 245	
AGG AGC CGG GCT GGG TCT CGG AAG CGG CCG CTG ACC CTG CTC CAG CGG	821
Arg Ser Arg Ala Gly Ser Arg Lys Arg Pro Leu Thr Leu Leu Gln Arg	
250 255 260	
GCG GGG CTG CTG CTA CTC TTG GGA CTG CTG GGC TTC CTG GCC CTC CTT	869
Ala Gly Leu Leu Leu Leu Leu Gly Leu Leu Gly Phe Leu Ala Leu Leu	
265 270 275 280	
GCC CTC ATG TCT CGC CTA GGC CGG GCC GCA GCT GAC AGC GAT CCC AAC	917
Ala Leu Met Ser Arg Leu Gly Arg Ala Ala Ala Asp Ser Asp Pro Asn	
285 290 295	
CTG GAC CCA CTC ATG AAC CCT CAC ATC CGC GTG GGC CCC TCC TGA	962
Leu Asp Pro Leu Met Asn Pro His Ile Arg Val Gly Pro Ser	
300 305 310	
GCCCCCTTGC TTGTGGCTAG GCCAGCCTAG GATGTGGGTT CTGTGGAGGA GAGGCGGGGT	1022
AATGGGGAGG CTGAGGGCAC CTCTTCACTG CCCCTCTCCC TCAAGCCTAA GACACTAAGA	1082
CCCCAGACCC AAAGCCAAGT CCACCAGAGT GGCTCGCAGG CCAGGCCTGG AGTCCCCGTG	1142
GGTCAAGCAT TTGTCTTGAC TTGCTTTCTC CCGGGTCTCC AGCCTCCGAC CCCTCGCCCC	1202
ATGAAGGAGC TGGCAGGTGG AAATAAACAA CAACTTTATT	1242

3/32

Figure 2

gb|AA155210|AA155210 mr98e01.r1 Stratagene mouse embryonic carcinoma
(#937317) Mus musculus cDNA clone 605496 5'

Query: 1 MGLCKCPKRKVTNLFCEHRVNVCEHCLVANHAKCIVQSYLQWLQDSDYNPNCRLCNIP 60
MGLCKCPKRKVTNLFCEHRVNVCEHCLVANHAKCIVQSYLQWLQDSDYNPNCRLCN PL
Sbjct: 38 MGLCKCPKRKVTNLFCEHRVNVCEHCLVANHAKCIVQSYLQWLQDSDYNPNCRLCNTPL 277

Figure 3

dbj|D75913|CELK111G3F C.elegans cDNA clone yk111g3 : 5' end. single read.

Query: 7 PKRKVTNLFCEHRVNVCEHCLVANHAKCIVQSYLQWLQDSDYNPNCRLCNIPASRETT 66
PKRKVTNLF +EHRVNVCE LV NH C+VQSYL WL D DY+PNC LC L +T
Sbjct: 1- PKRKVTNLFXYEHRVNVCELVNHNHNCVVQSYLTWLTQDQYDPNCSLCKXTTLXEGDTI 180

Query: 67 RLVCYDLFWACLNERAAQLPRNTAPAGYQCP 98 98 PSCNGPIFPFNQ 109
RL C L HW C +E P TAP GY+CP P C+ +FPP+Q
Sbjct: 181 RLNCLHLLHWKCFDEWGXGNFPDPTAPXGYRCP 276 275 PCCSQEVFPPDQ 310

Figure 4

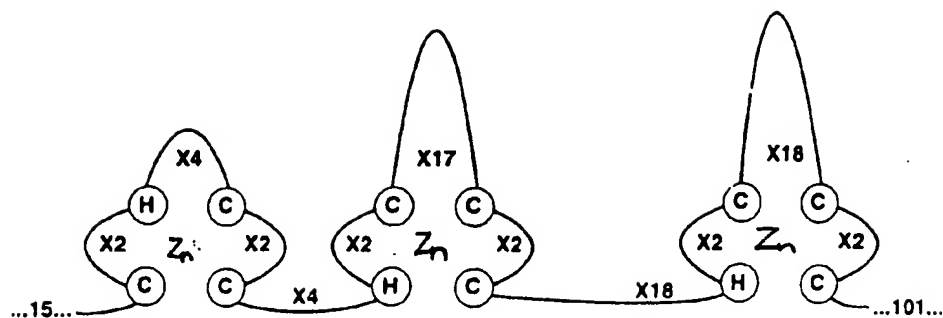


Figure 5

sp|P46580|YLB5_CAEEL HYPOTHETICAL 146.8 KD PROTEIN C34E10.5 IN
CHROMOSOME III gi|500728 (U10402) C34E10.5 gene product
[Caenorhabditis elegans]

Query: 56 CNIPLASRETTTRLVCYDLFWACLNERRAAQLPRNTAPAGYQCPSC 100
C+I L ++ + L C L F W C+ E A + + + +CP C
Sbjct: 1222 CSICLENKNPSALFCGHLFCWTCIQEHAVAATSSASTSSARCPQC 1266

Figure 6

gi|703468 (L29051) homologous to GATA-binding transcription factor
[Schizosaccharomyces pombe]

Query: 35 CIVQSYLQWLQDSYDNPNCRLCNI 58
C + +W +D NP C C +
Sbjct: 175 CATTNTPKWRRDESGNPICNACGL 198

Query: 162 SSTFGPEEVDSSAAPAFYSQAPRPPASPGRPEQHTVIHMCNPEPLTHAPRKVYDTRDDD 221
+S PEE S S S P+ SP + +Q +I P +V + D
Sbjct: 441 ASLLNPPEPPSNQPSMSNGPKSEVSPSQQAPLIQSSTSPVSLQFPPEVQGSNVOK 500

Query: 222 RTPGLH 227
R L+
Sbjct: 501 RNYALN 506

Figure 7



Score = 818 (226.0 bits), Expect = 6.1e-103, Sum P(5) = 6.1e-103
Identities = 206/259 (79%), Positives = 206/259 (79%), Strand = Plus / Plus

```

Query:      686 AAGGTGTATGATACGCGG 704
              || || ||||| || | ||
Sbjct:      289 AAAGTATATGACACACCGG 307

```

Score = 175 (48.4 bits), Expect = 6.1e-103, Sum P(5) = 6.1e-103
Identities = 39/44 (88%), Positives = 39/44 (88%), Strand = Plus / Plus

Score = 139 (38.4 bits), Expect = 6.1e-103, Sum P(5) = 6.1e-103
Identities = 31/35 (88%), Positives = 31/35 (88%), Strand = Plus / Plus

Score = 133 (36.8 bits), Expect = 6.1e-103, Sum P(5) = 5.1e-103
Identities = 29/32 (90%), Positives = 29/32 (90%), Strand = Plus / plus

```
Query:      701 CCGGATGATGACCGGACACCAGGCCTCCATGG      732
             |||||
Sbjct:      305 CCGGATGATGACCGGACAGCAGGCATTTCATGG      336
```

Figure 8 continued

gb|AA134788|AA134788 zm81g02.r1 Stratagene neuroepithelium (#937231)
Homo sapiens cDNA clone 532082 5'
Length = 368

Plus Strand HSPs:

Score = 563 (155.6 bits), Expect = 3.8e-87, Sum P(3) = 3.8e-87
Identities = 147/190 (77%), Positives = 147/190 (77%), Strand = Plus / plus

[illegible]

Score = 454 (125.4 bits), Expect = 3.8e-87, Sum P(3) = 3.8e-87
Identities = 94/98 (95%), Positives = 94/98 (95%), Strand = Plus / Plus

```

Query:   398  GCACTGAGAGAGAAGCTGGCCACAGTCAACTGGGCCCGGGCAGGACTGGGCCTCCCTCTG  457
          |||
Sbjct:    2   GCACTGAGAGACAAGCTAGCCACAGTCAACTGGGCCCGGGCAGGACTGGGCCTCCCTCTG  61
          .
Query:   458  ATCGATGAGGTGGTGAGCCAGAGCCCGAGCCCTCAA  495
          |||
Sbjct:   62  ATCGATGAGGTGATAAGCCAGAGCCCGAGCCCTCAA  99

```

Score = 219 (60.5 bits), Expect = 3.8e-87, Sum P(3) = 3.8e-87
Identities = 51/60 (85%), Positives = 51/60 (85%), Strand = Plus / Plus

Query: 702 GGGATGATGACCGGACACCGCCCTCCATGGAGACTGTGACGATGACAAGTACCGACGTC 761
 |||
 Sbjct: 309 GGA TTGATGACCGGACAGCAGGCATTCATGGAGACTGTGATGATGACA AATACCGCCGCC 368

Figure 9

W32939 human TACCGCCCTTCGGAACCACTGCAGCGGCCGATCAGTAAACACAGAGACTGGGGATCGATCATGGGGCTTTTGTAAAG
AA242159 mouse CTTCCCGCGCTTTTCATTACCGTACGCACCGGTCA-CGATCGGCATCGCGAGGATGGTCAATGGACTTTTGC AAG

FIGURE 10

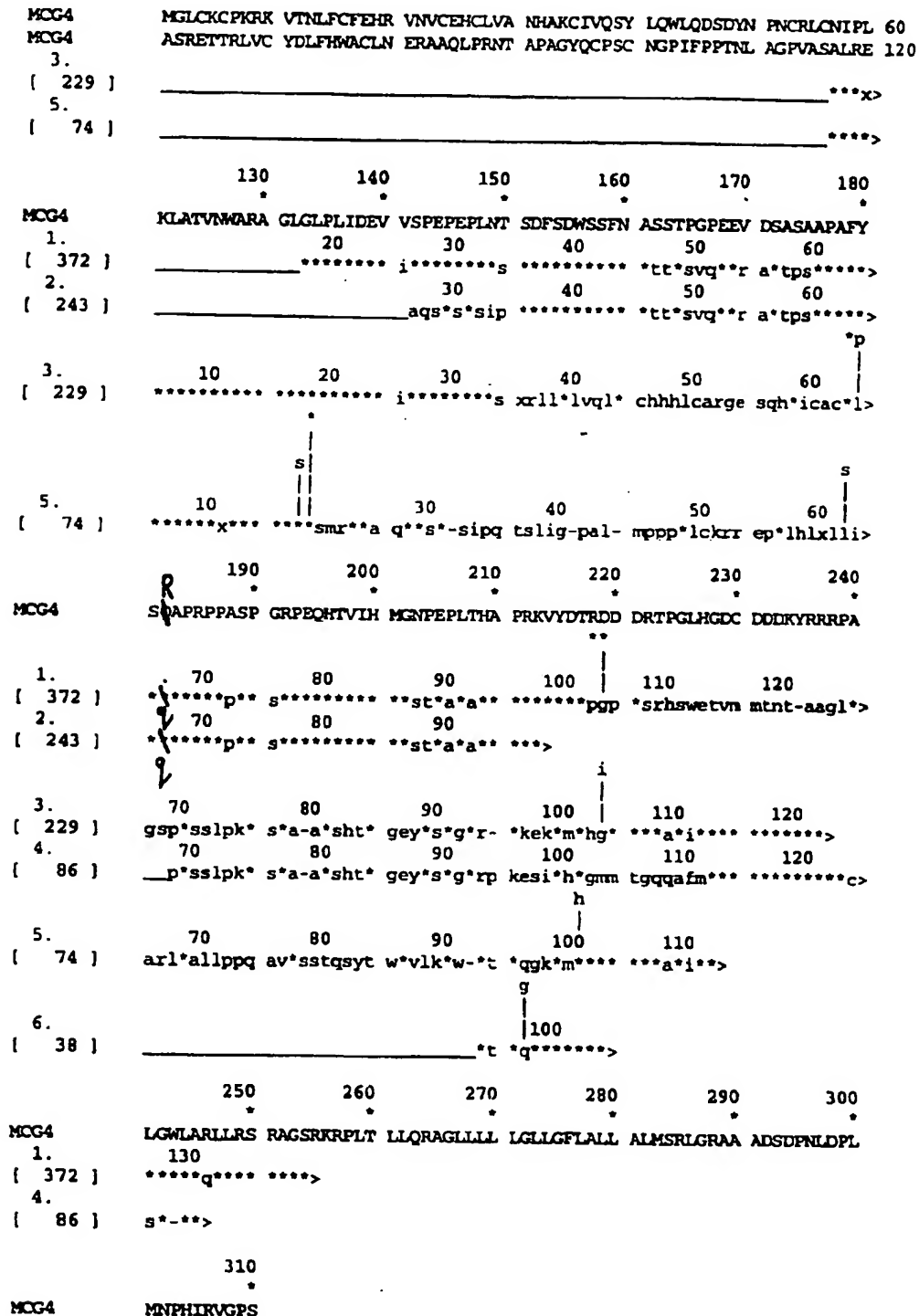


Figure 10 (Continued)

Search Analysis for Sequence: MCG4

Matrix: pam250 matrix

Search from 1 to 310

Score Region from 1 to 310

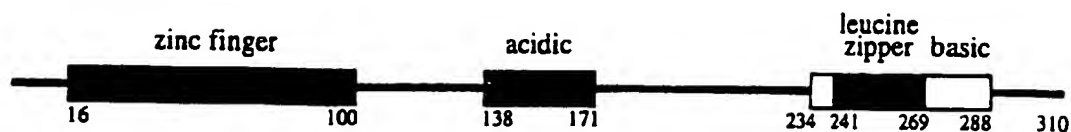
Date: September 22, 1997

Maximum possible score: 1598

Aligned sequences:

1. = EST AA074703 phase 1 translation
2. = EST AA134788 phase 3 translation
3. = EST AA134788 phase 2 translation
4. = EST AA074703 phase 3 translation
5. = EST AA074703 phase 2 translation
6. = EST AA134788 phase 1 translation

FIGURE 11 Domains of MCG4



zinc finger consensus: $CX_2HX_4CX_2CX_4HX_2CX_{17}CX_2CX_{18}HX_2CX_{18}CX_2C$

acidic domain consensus: 9/34 negatively charged amino acids, 0/34 positively charged

basic domain consensus: 13/55 positively charged amino acids, 0/55 negatively charged

leucine zipper domain consensus: $LX_6LX_6RX_6LX_6L$

alternate "novel" leucine zipper-like motif where leucine would not be aligned along the one surface of an alpha helix domain: (aa 261) $LX_6LXLX_6LXLX_6L$ (aa 286)

FIGURE 12

Sequences producing High-scoring Segment Pairs:		High Score	Smallest Sum Probability P(N)	N
gnl PID e236178	(270752) F25B3.3 (Caenorhabditis ele...	307	3.0e-124	8
gi 1293099	(U53884) aimless RasGEF [Dictyosteli...	202	7.8e-22	5
gi 1655941	(U67326) Ras-GRF2 [Mus musculus]	152	3.6e-16	4
pir S30356	CDC25 protein homolog - yeast (Candi...	150	2.2e-15	3
sp P43069 CC25_CANAL	CELL DIVISION CONTROL PROTEIN 25	150	2.2e-15	3
sp P28818 GNRP_RAT	GUANINE NUCLEOTIDE RELEASING PROTEIN...	166	2.6e-15	3
prf 1814463A	guanine nucleotide-releasing factor ...	166	2.6e-15	3
pir B46199	nucleotide-exchange-factor homolog c...	167	1.1e-14	1
gnl PID e238680	(X97560) hypothetical protein L1309 ...	158	3.0e-14	3
pir S22693	CDC25 protein homolog - mouse /gi 50...	167	3.7e-14	2
sp P14771 SC25_YEAST	SCD25 PROTEIN /gi 457494 (M26647) SD...	158	4.6e-14	3
sp P26674 STE6_SCHPO	STE6 PROTEIN /pir S28098 ste6 prote...	160	5.2e-14	2
pir S28407	CDC25 protein homolog - mouse	167	1.2e-13	3
sp P27671 GNRP_MOUSE	GUANINE NUCLEOTIDE RELEASING PROTEIN...	167	1.2e-13	3
gi 386047	(S62035) Ras-specific guanine nucleo...	153	2.0e-13	2
sp Q02342 CC25_SACKL	CELL DIVISION CONTROL PROTEIN 25 /pi...	142	4.5e-13	2
pir S14177	SCD25 protein - yeast (Saccharomyces...	152	5.7e-13	3
gi 433720	(L26584) CDC25 [Homo sapiens]	153	6.0e-13	3
gnl PID e241744	(268880) T14G10.2 [Caenorhabditis el...	157	7.2e-13	1
gi 3484	(X03579) CDC25 protein (aa 1-1588) [...	136	3.4e-12	3
sp P04821 CC25_YEAST	CELL DIVISION CONTROL PROTEIN 25 /pi...	136	3.4e-12	3
gi 915328	(U24070) Munc13-1 [Rattus norvegicus]	151	5.5e-12	1
pir A46199	nucleotide-exchange-factor homolog c...	149	5.6e-12	1
pdb 1PTR	Molecule: Protein Kinase C Delta Ty...	136	1.5e-11	1
gi 915330	(U24071) Munc13-2 [Rattus norvegicus]	150	1.6e-11	2
gi 474982	(D21239) 'C3G protein' [Homo sapiens...	131	3.3e-11	3
gi 1763306	(U75361) Munc13-3 [Rattus norvegicus]	153	6.4e-11	2
gi 806957	guanine-nucleotide exchange factor C...	128	7.8e-11	3
sp Q03385 GNDS_MOUSE	GUANINE NUCLEOTIDE DISSOCIATION STIM...	133	1.0e-10	2
pir BVBYL1	LTE1 protein - yeast (Saccharomyces ...	139	1.9e-10	1
gi 452242	(D21354) a putative guanine nucleoti...	139	2.7e-10	1
sp P07866 LTE1_YEAST	LOW TEMPERATURE ESSENTIAL PROTEIN /p...	139	2.7e-10	1
gi 509050	(Z22521) protein kinase C delta (Hom...	137	4.0e-10	1
gi 520587	(D10495) protein kinase C delta-type...	137	4.6e-10	1
sp P05130 KPC1_DROME	PROTEIN KINASE C, BRAIN ISOZYME (PKC...	137	4.7e-10	1
pir S35704	protein kinase C (EC 2.7.1.-) delta ...	137	4.7e-10	1
sp Q05655 KPCD_HUMAN	PROTEIN KINASE C, DELTA TYPE (NPKC-D...	137	4.7e-10	1
pir S40279	protein kinase C mu - human /pir A5...	137	4.9e-10	1
sp P09215 KPCD_RAT	PROTEIN KINASE C, DELTA TYPE (NPKC-D...	135	9.0e-10	1
gi 520878	(Z34524) serine/threonine protein ki...	133	1.8e-09	1
gi 1519719	(U68142) RalGDS-like [Homo sapiens]	115	3.8e-09	3

12/32

FIGURE 13(a) (i)

MCG7 - Cloning of a novel human gene that encodes a guanine exchange factor

CGATTTCATTCCTCGCTCCCCACAGGTCCTCTCCCCAAAATATTCCTCATCTTGTCTAG 60
I S F L A P H R S L S P K Y S H L V L 19
CCCATCCCCCAGACTATCTCAAGGACCAGCTGTCCCCACGCCCCGACCTCCACTAGGCC 120
A H P P D Y L K D Q L S P R P R P P L G 39
TGTGCCACCCGCTGCCTGCAGGAAGACGCCCGGTCCCGGGCCGGGTTAGCCCCATGGGAA 180
L C H P L P A G R R P V P G R V S P M G 59
CGcagcgctgtgtggccgcgggactcaaggctggcctggctcaagtgaacagcacgtcc 240
T Q R L C G R G T Q G W P G S S E Q H V 79
aggagggcgacctcgtccgcggtttgcattctggggtggacgagctggGGGTTCGGTCCG 300
Q E A T S S A G L H S G V D E L G V R S 99
AGCCCGGTGGGAGGCTCCCGGAGCGCAGCTGGGCCCAGCCACCCCGCGCCGGCGCC 360
E P G G R L P E R S L G P A H P A P A A 119
TGGCAGGCACCTGGACCTGGACAAGGGCTGCACGGTGGAGGAGCTGCTCCGCGGGTGCA 420
M A G T L D L D K G C T V E E L L R G C 139
TCGAAGCCTTCGATGACTCCGGAAGGTGCGGGACCCGAGCTGGTGCATGTTCTCTCA 480
I E A F D D S G K V R D P Q L V R M F L 159
TGATGCACCCCTGGTACATCCCCCTCTCTCAGCTGGCGGCCAAGCTGCTCCACATCTACC 540
M M H P W Y I P S S Q L A A K L L H I Y 179
AACAAATCCCGGAAGGACAACCTCAATTCCTGTCAGGTGAAAACGTGCCACCTGGTCAGGT 600
Q Q S R K D N S N S L Q V K T C H L V R 199
ACTGGATCTCCGCTTCCAGCGGAGTTTGACTTGAACCCGGAGTTGGCTGAGCAGATCA 660
Y W I S A F P A E F D L N P E L A E Q I 219
AGGAGCTGAAGGCTCTGCTAGACCAAGAAGGGAACCGACGGCACAGCAGCCTAATCGACA 720
K E L K A L L D Q E G N R R H S S L I D 239
TAGACAGCGTCCCTACCTACAAGTGGAAGCGGCAGGTGACTCAGCGGAACCCCTGTGGGAC 780
I D S V P T Y K W K R Q V T Q R N P V G 259
AGAAAAAGCGCAAGATGTCCCTGTTGTTTGACCACCTGGAGCCCATGGAGCTGGCGGAGC 840
Q K K R K M S L L F D H L E P M E L A E 279
ATCTCACCTACTTGGAGTATCGCTCCTTCTGCAAGATCCTGTTTCAGGACTATCACAGTT 900
H L T Y L E Y R S F C K I L F Q D Y H S 299
TCGTGACTCATGGCTGCACTGTGGACAACCCCGTCTCTGGAGCGGTTTCATCTCCCTCTTCA 960
F V T H G C T V D N P V L E R F I S L F 319
ACAGCGTCTCACAGTGGGTGCAGCTCATGATCCTCAGCAAACCCACAGCCCCGCGCGGG 1020
N S V Q W V Q L M I L S K P T A P Q R 339
CCCTGGTTCATCACACACTTTGTCCACGTGGCGGAGAAGCTGCTACAGCTGCAGAACTTCA 1080
A L V I T H F V H V A E K L L Q L Q N F 359
ACACGCTGATGGCAGTGGTGGGGGCTGAGCCACAGCTCCATCTCCCGCTCAAGGAGA 1140
N T L M A V V G G L S H S S I S R L K E 379
CCCACAGCCACGTTAGCCCTGAGACCATCAAGCTCTGGGAGGGTCTCACGGAACCTAGTGA 1200
T H S H V S P E T I K L W E G L T E L V 399
CGGCGACAGGCAACTATGGCAACTACCGGCGTGGGCTGGCAGCCTGTGTGGGCTTCCGCT 1260
T A T G N Y G N Y R R R L A A C V G F R 419
TCCCGATCCTGGGTGTGCACCTCAAGGACCTGGTGGCCCTGCAGCTGGCACTGCCTGACT 1320
F P I L G V H L K D L V A L Q L A L P D 439
GGCTGGACCCAGCCCGGACCCGGCTCAACGGGGCCAAGATGAAGCAGCTCTTTAGCATCC 1380
W L D P A R T R L N G A K M K Q L F S I 459
TGGAGGAGCTGGCCATGGTGACCAGCCTGCGGCCACCAAGTACAGGCCAACCCCGACCTGC 1440
L E E L A M V T S L R P P V Q A N P D L 479
TGAGCCTGCTCACGGTGTCTCTGGATCAGTATCAGACGGAGGATGAGCTGTACCAGCTGT 1500
L S L L T V S L D Q Y Q T E D E L Y Q L 499
CCCTGCAGCGGGAGCCCGCTCCAAGTCCCTCGCCAACCCAGCCCCACGAGTTGCACCCAC 1560
S L Q R E P R S K S S P T S P T S C T P 519
CACCCCGGCCCCCGTACTGGAGGAGTGGACCTCGGCTGCCAAACCCAAGCTGGATCAGG 1620
P P R P P V L E E W T S A A K P K L D Q 539
CCCTCGTGGTGGAGCACATCGAGAAGATGGTGGAGTCTGTGTTCCGGAACCTTGACGTCG 1680

FIGURE 13(a) (ii)

A L V V E H I E K M V E S V F R N F D V 559
ATGGGGATGGCCACATCTCACAGGAAGAATTCCAGATCATCCGTGGGAACCTTCCCTTACC 1740
D G D G H I S Q E E F Q I I R G N F P Y 579
TCAGCGCCTTTGGGGACCTCGACCAGAACCAGGATGGCTGCATCAGCAGGGAGGAGATGG 1800
L S A F G D L D Q N Q D G C I S R E E M 599
TTTCCTATTTCTGCGCTCCAGCTCTGTGTTGGGGGGCGCATGGGCTTCGTACACAACT 1860
V S Y F L R S S S V L G G R M G F V H N 619
TCCAGGAGAGCAACTCCTTGCGCCCCGTGCGCTGCCGCACTGCAAAGCCCTGATCCTGG 1920
P Q E S N S L R P V A C R H C K A L I L 639
GCATCTACAAGCAGGGCCTCAAATGCCGAGCCTGTGGAGTGAAGTCCACAAGCAGTGCA 1980
G I Y K Q G L K C R A C G V N C H K Q C 659
AGGATCGCCTGTGAGTTGAGTGTGCGGCGCAGGGCCCAGAGTGTGAGCCTGGAGGGGTCTG 2040
K D R L S V E C R R R A Q S V S L E G S 679
CACCCCTCACCCCTCACCCATGCACAGCCACCATCACCGCGCCTTCAGCTTCTCTGCCCC 2100
A P S P S P M H S H H H R A F S F S L P 699
GCCCTGGCAGGCGAGGCTCCAGGCCTCCAGAGATCCGTGAGGAGGAGGTACAGACGGTGG 2160
R P G R R G S R P P E I R E E E V Q T V 719
AGGATGGGGTGTGTTGACATCCACTTGTAAATAGATGCTGTGGTTGGATCAAGGACTCATT 2220
E D G V F D I H L * 728
CTGCCTTGGAGAAAATACTTCAACCAGAGCAGGGAGCCTGGGGGTGTGCGGGCAGGAGGC 2280
TGGGGATGGGGGTGGGATATGAGGGTGGCATGCAGCTGAGGGCAGGGCCAGGGCTGGTGT 2340
CCCTAAGGTTGTACAGACTCTTGTGAATATTTGTATTTTCCAGATGGAATAAAAAGGCC 2400
GTGTAATTAACCTTC(A)_n

14/32

FIGURE 13(b)

CGATTTTCATTCTCGCTCCCCACAGGTCCCTCTCCCCAAAATATTCCTATCTTGTCTTAG 60
CCCATCCCCCAGACTATCTCAAGGACCAGCTGTCCCCACGCCCCCGACCTCCACTAGGCC 120
TGTGCCACCCGCTGCCTGCAGGAAGACGCCCCGGTCCCGGGCCGGGTTAGCCCATGGGAA 180
* p h g n
CGGGGTTCGGTCCGAGCCCCGGTGGGAGGCTCCCGGAGCGCAGCCTGGGCCCAGCCACCC-240
g v r s e p g g r l p e r s l g p a h p
CGCGCCGGCGGCCATGGCAGGCACCCTGGACCTGGACAAGGGCTGCACGGTGGAGGAGCT-300
a p a a M A G T L D L D K G C T V E E L

```

1 MAGTLDLKDGC...TVEELRGCI EAF...DDSGKVRDPQLVRFMLMHPW 45
|.:.:|. |.:|: |:| |.:.| |:| :.:|. |
1 MSSKVEEDQHQELLTEDQLVARCVECFVDVEEDEVEDIEFVDALFLSHQ 50
. . . . .
46 YIPSSQLAAKLHLHIYQQSRKDNSNSLQVKTCHELVRYWISAFFAEFDLNPE 95
. | | .:..:|:|. . . . |:|:|. | .|| .:|
51 LSDSLSLITHFVNIFYQETRNVQRE...AVCRVSFWIEKFPMHFDAQPO 97
. . . . .
96 LAEIQIKELKALLDQEGNRRHSSLIDIDSVPPTYKWKRQVTQRNPVGQKK.. 143
.:|: ||.: : .: .:| |.:|:|. | |. | |.:...
98 VCAQVVRLKTIAEDINENIRNGL.DVSALPSPFAWLRAVSVRNPLAKQTIV 146
. . . . .
144 .....RKMSLLFDHLEPMELAEHLTLYLEYR 168
:| | : .| :.. |.:|
147 RVDFTETLPTPGTPPPFPPIASKKFSLTAFSLSFVQASPSDISTSLSHIDYR 196
. . . . .
169 SFCKILFQDYHSFVTHGCTVDNPVLERFISLFNSVSQWVQMILSKPTAP 218
.:|: | .: .:|. | .|:| | |.:|:|. | |. | |.:
197 VLSRISITELKQYVKDGHLRSCPMLESI SVFNNL SNWVQCMI LNKTTPK 246
. . . . .
219 QRALVITHEFHVAEKLLLOLONENTLMNAVVGGLSHSSISRLKETHSHVSPE 268
:| | :..:| | |. | .|:| | | |.:|:|. | |. | |.:
247 ERAEILVKFHVHAKHLRKINNENTLMSVVGGITSSVARLAITYAVLSND 296
. . . . .
269 TIKLWEGLTELVTATGNYGNYRRRLAAC.VGFRFPILGVHLKDLVALOLA 317
. | .:|:|. | |.:|:|. |:| |.:|:| | | |.:.
297 IKKELTQLTNLLSAQHNFCEYRKALGACNKKFRIPIIGVHLKDLVAINCS 346
. . . . .
318 LPDWLDPARTRLNGAKMKQLFSILEELAMVTSLRPPV.QANPDLLSLLTV 366
.:. . .:|:|. | .:|:|. . . . . | |.:|. |
347 GANFEKT..KCISSDKLVKLSKLLSNFLVFNQKHNLPEMNMDLINTLKV 394
. . . . .
367 SLDQYQTEDELYQLSLQREPRSKSSPTSPTSCTPPPRPPVLEEWSAACP 416
||| .:|:|. | |.:|:|. . . . |. |. |.:|:|.
395 SLDIRYNODDIYELSLRREP KTFMN.....FEPSRGLVFAEWASGVTV 437
. . . . .
417 KLDQALVVEHIEKMVESVFRNFVDGDGHISOEEFQIIRGNFYLSAFGD 466
|. | |. | |.:|:|. | | | | | | | | | |.:|:|.
438 APDNATVSKHISAMVDAVFKHYDHDROGFISOEEFQLIAGNFFPIDAFVN 487
. . . . .
467 LDONODGCISREEMVSYFLRSS.SVLGGRMGFVHNFOESNSLRPVACRHC 515
:| : | |.:|:|. | |.:. . . : |. | | |.:|. | |. | |
488 IDVDMDOISKDELKTYFMAANKNTKDLRRGFKHNHETTFLTPTTCNHCH 537
. . . . .
516 KALILGIYKOGLKCRACGVNCHKOCKDRLSVECCRRAQSVSLEGSAPSPTS 565
. |.:|:|. | |.:|:|. | |. . | | |.:|. | .: .:|
538 NKLLWGILROGFKCKDCGLAVHSCCKSNAVAECRRKSSSNLTRAAEFWAS 587
. . . . .
566 PMSHHHHRAFSSFLRPGRGRSRPPEIREEEVQTVEDGVDFIHL 609
|. |:|:|. .:|:|. |. | |. | |.:|:|. |
588 PRGSMRSRIINTC....NMSGSTPDEEIGLVSLACEEVFEDDDL 627
. . . . .

```

FIGURE 15

```

human      CGATTTCATT CCTCGCTCCC CACAGGTCCC TCTCCCCAAA ATATTCCCAT CTGTCTCTAG 60
human      CCCATCCCCC AGACTATCTC AAGGACCAGC TGTCCCCACG CCCCCGACCT CCACTAGGCC 120
human      TGTGCCACCC GCTGCCTGCA GGAAGACGCC CGGTCCCGGG CCGGGTTAGC CCCATGGGAA 180
human      CGCAGCGCCT GTGTGGCCGC GGGACTCAAG GCTGGCCTGG CTCAAGTGAA CAGCACGTCC 240
mouse      ***tcag** ***ag*** t***** **a*g***t>
human      AGGAGCGGAC CTCGTCCGCG GGTTCGCATT CTGGGGTGGA CGAGCTGGGG GTTCGGTCCG 300
                                     acagg
                                     |
mouse      g*****t**a **-catt** ***** ***aa**aa* g**ct***** **a**aat**>
human      AGCCCGGTGG GAGGCTCCCG GAGCGCAGCC TGGGCCACGC CCACCCCGCG CCGGCGGCCA 360
mouse      ***a*t**** *****tga ***t*t*a*t ***t*t*** ***-tg**a *****a****>
human      TGGCAGGCAC CCTGGACCTG GACAAGGGCT GCACGGTGGA GGAGCTGCTC CGCGGGTGCA 420
mouse      ***ga**** t***** *****t* ***c***** ***** **t*c**t*>
human      TCGAAGCCTT CGATGACTCC GGAAGGTGC GGGACCCGCA GCTGGTGC GC ATGTTCTCTCA 480
mouse      *****t*****t **a***** *a**t**a** ***a***** *****t*****>
human      TGATGCACCC CTGGTACATC CCCTCCTCTC AGCTGGCGGC CAAGCTGCTC CACATCTACC 540
mouse      *****a **t***** *****tt* g**a***** ***t*****t*>
human      AACAATCCCG GAAGGACAAC TCCAATTCCT TGCAGGTGAA AACGTGCCAC CTGGTCAGGT 600
mouse      *g***** *****t* *a***a*** *****t*** *****t*****>
human      ACTGGATCTC CGCCTTCCCA GCGGAGTTTG ACTTGAACCC GGAGTTGGCT GAGCAGATCA 660
mouse      *****a***** **a*****a***** a**c***** **a*****>
human      AGGAGCTGAA GGCTCTGCTA GACCAAGAAG GGAACCGACG GCACAGCAGC CTAATCGACA 720
mouse      *****t** ***** *****ca* ***** **c*****>
human      TAGACAGCGT
mouse      *c**g**t**

```

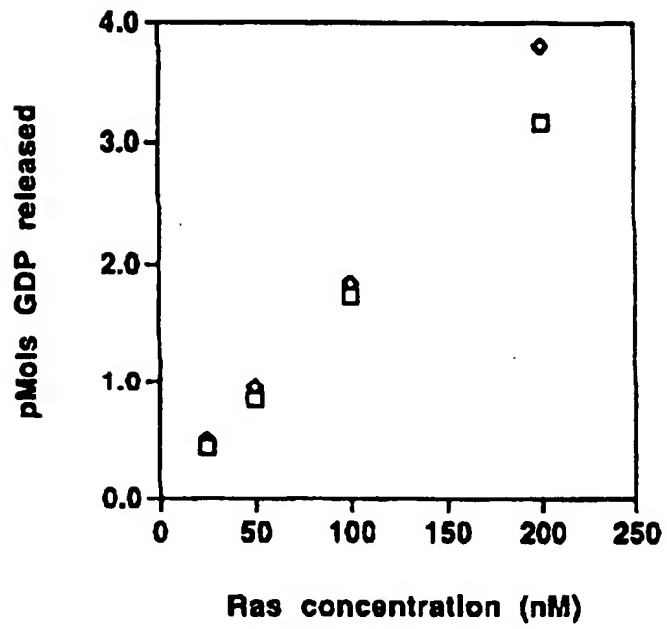
17/32

FIGURE 16

CACGCCTCGGAAGGGAGGTTTGGGGTCGGTGGTTTACAGTGAGTGTGTCTGAAGCCAAA 60
TGGTCGGAAACCGTTACCCGCTCTCCTAGGCCCGGCTAGTGGGGACCCCAACCGCCTGCG 120
* A R L V G T P T A C>
GCTGCCCCCTCCCAAGTTCCTCCCTGTTGGCCAGGCATCCAGGTCTCCAGTCTCCGAGCTG 180
G C P S Q V P P C W P G I Q V S S L R A>
CGGAGAACCACCGCCACATGCGGCTGCCCCTTTCCATTGACCCCTGTGGGGAGCCAGGC 240
A E N P P P H A A A P F H S T L W G A R>
TTCGGGGCCCCGTTCTCTGTGTGAAGTGGGCCCCCGCCCCATTCCAGACATCAA 300
L P G P R S S C V N W A P R P H S Q T S>
GGCCGCGTCTCCAGATAGCCACGATTTTCATTCCTCGCTCCCCACAGGTCCCTCTCCCCAA 360
R P R L Q I A T I S F L A P H R S L S P>
AATATTCCCATCTTGTCTAGCCCATCCCTCAGACTATCTCAAGGACCAGCTGTCCCCAC 420
K Y S H L V L A H P P D Y L K D Q L S P>
GCCCCGACCTCCACTAGGCCTGTGCCACCCGCTGCCTGCAGGAAGACGCCCGGTCCCGG 480
R P R P P L G L C H P L P A G R R P V P>
GCCGGGTTAGCCCCATGGGAACGcagcgccctgtgtggccgcgggactcaaggctggcctg 540
* p h g n
G R V S P M G T Q R L C G R G T Q G W P>
gctcaagtgaacagcacgtccaggaggcgacctcgccgcggtttgcattctggggtgg 600
G S S E Q H V Q E A T S S A G L H S G V>
acgagctggGGTTTCGGTCCGAGCCCGGTGGGAGGCTCCCGGAGCGCAGCCTGGGCCCAG 660
D E L G V R S E P G G R L P E R S L G P>
CCCACCCCGCGCCGGCGGCCATGGCAGGCACCCCTGGACCTGGACAAGGGCTGCACGGTGG 720
A H P A P A A M A G T L D L D K G C T V>

18/32

FIGURE 17



19/32

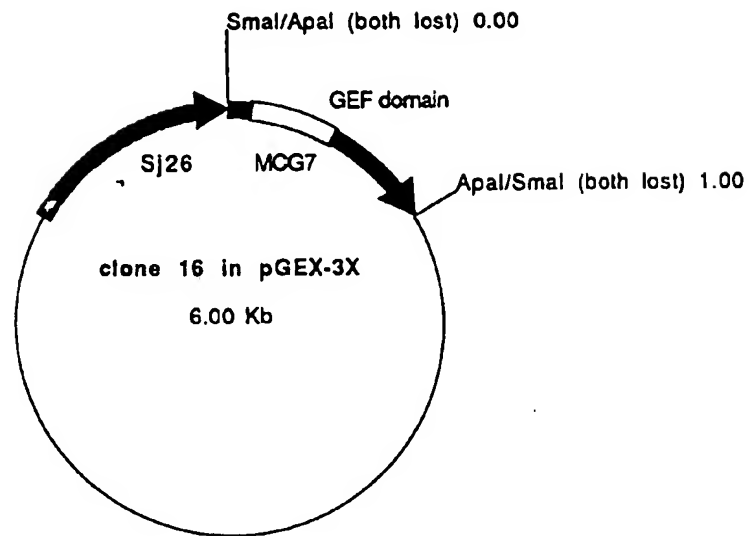
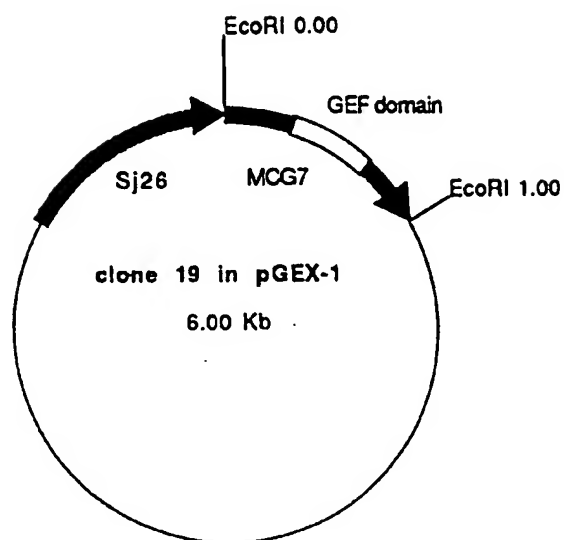
FIGURE 18 (Cont. I)**Plasmid name:** clone 16 in pGEX-3X**Plasmid size:** 6.00 kb

FIGURE 18 (Cont. II)

Plasmid name: clone 19 in pGEX-1

Plasmid size: 6.00 kb

21/32

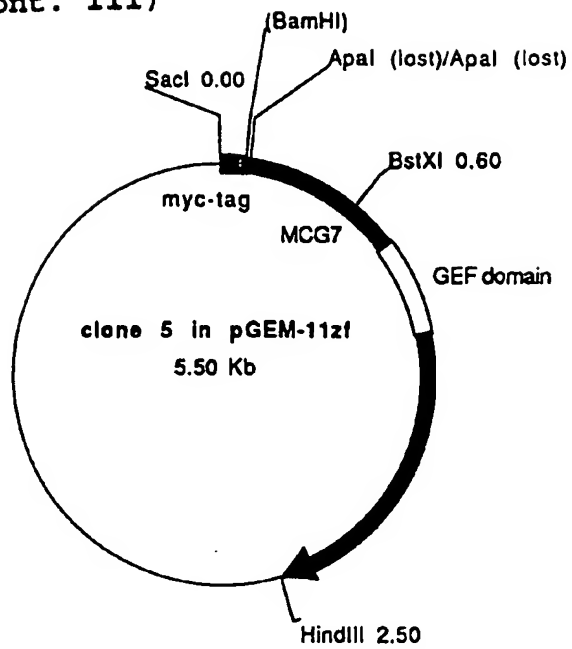
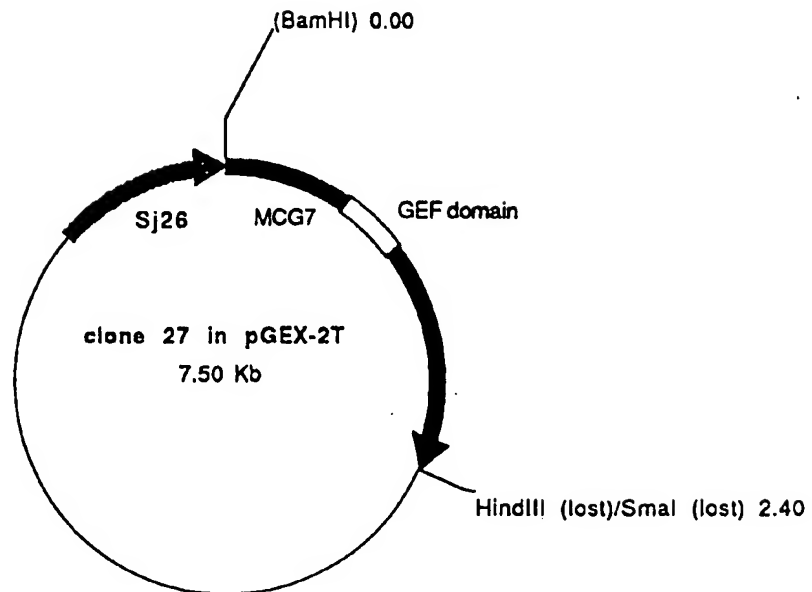
FIGURE 18 (Cont. III)**Plasmid name:** clone 5 in pGEM-11zf**Plasmid size:** 5.50 kb

FIGURE 18 (Cont. IV)

Plasmid name: clone 27 in pGEX-2T

Plasmid size: 7.50 kb

23/32

FIGURE 19

GCCCCGCCGCC															ATG	CGC	CCC	TTA	CTG	CCC	CTG	CGC	CTG	TGC	CGG	CTG	TGG	49		
															Met	Pro	Pro	Leu	Leu	Pro	Leu	Arg	Leu	Cys	Arg	Leu	Trp			
															1					5					10					
CCC	CGC	AAC	CCT	CCC	TCC	CGG	CTC	CTC	GGA	GCG	GCC	GCC	GGG	CAG	CGG	97														
Pro	Arg	Asn	Pro	Pro	Ser	Arg	Leu	Leu	Gly	Ala	Ala	Ala	Gly	Gln	Arg															
															15				20			25								
TCC	AGA	CCC	AGT	ACT	TAT	TAT	GAA	CTG	TTG	GGG	GTG	CAT	CCT	GGT	GCC	145														
Ser	Arg	Pro	Ser	Thr	Tyr	Tyr	Glu	Leu	Leu	Gly	Val	His	Pro	Gly	Ala															
															30				35			40		45						
AGC	ACT	GAG	GAA	GTT	AAA	CGA	GCT	TTC	TTC	TCC	AAG	TCC	AAA	GAG	CTG	193														
Ser	Thr	Glu	Glu	Val	Lys	Arg	Ala	Phe	Phe	Ser	Lys	Ser	Lys	Glu	Leu															
																		50			55		60							
CAC	CCA	GAC	CGG	GAC	CCT	GGG	AAC	CCA	AGC	CTG	CAC	AGC	CGC	TTT	GTG	241														
His	Pro	Asp	Arg	Asp	Pro	Gly	Asn	Pro	Ser	Leu	His	Ser	Arg	Phe	Val															
																		65			70		75							
GAG	CTG	AGC	GAG	GCA	TAC	CGT	GTG	CTC	AGC	CGT	GAG	CAG	AGC	CGC	CGC	289														
Glu	Leu	Ser	Glu	Ala	Tyr	Arg	Val	Leu	Ser	Arg	Glu	Gln	Ser	Arg	Arg															
																	80				85		90							
AGC	TAT	GAT	GAC	CAG	CTC	CGC	TCA	GGT	AGT	CCC	CCA	AAG	TCT	CCA	CGA	337														
Ser	Tyr	Asp	Asp	Gln	Leu	Arg	Ser	Gly	Ser	Pro	Pro	Lys	Ser	Pro	Arg															
																	95				100		105							
ACC	ACA	GTC	CAT	GAC	AAG	TCT	GCC	CAC	CAA	ACA	CAC	AGC	TCC	TGG	ACA	385														
Thr	Thr	Val	His	Asp	Lys	Ser	Ala	His	Gln	Thr	His	Ser	Ser	Trp	Thr															
																				110		115		120						
CCC	CCC	AAC	GCA	CAG	TAC	TGG	TCC	CAG	TTT	CAC	AGC	GTG	AGG	CCA	CAG	433														
Pro	Pro	Asn	Ala	Gln	Tyr	Trp	Ser	Gln	Phe	His	Ser	Val	Arg	Pro	Gln															
																				130			135							
GGG	CCC	CAG	TTG	AGG	CAG	CAG	CAA	CAC	AAA	CAA	AAC	AAA	CAA	GTG	CTG	481														
Gly	Pro	Gln	Leu	Arg	Gln	Gln	Gln	His	Lys	Gln	Asn	Lys	Gln	Val	Leu															
																				145		150		155						
GGG	TAC	TGC	CTC	CTC	CTC	ATG	CTG	GCG	GGC	ATG	GGC	CTG	CAC	TAC	ATT	529														
Gly	Tyr	Cys	Leu	Leu	Leu	Met	Leu	Ala	Gly	Met	Gly	Leu	His	Tyr	Ile															
																	160				165		170							
GCC	TTC	AGG	AAG	GTG	AAG	CAG	ATG	CAC	CTT	AAC	TTC	ATG	GAT	GAA	AAG	577														
Ala	Phe	Arg	Lys	Val	Lys	Gln	Met	His	Leu	Asn	Phe	Met	Asp	Glu	Lys															
																	175				180		185							
GAT															CGG	ATC	ATC	ACA	GCC	TTC	TAC	AAC	GAA	GCC	CGG	GCA	CGG	GCC	AGG	625

[illegible]

FIGURE 20

```
>sp|P08622|DNAJ_ECOLI DNAJ PROTEIN >pir||HHECDJ heat shock protein dnaJ -  
Escherichia coli >gi|145769 (M12565)-heat shock protein dnaJ  
(Escherichia coli) >gi|216441 (D10483) dnaJ protein [Escherichia  
coli]  
Length = 376
```

```
Score = 138 (63.7 bits), Expect = 1.2e-10, P = 1.2e-10  
Identities = 25/62 (40%), Positives = 39/62 (62%)
```

```
Query:   35 YYELLGVHPGASTEEVKRAFFSKSKELHPDRDPGNPSLHSRFVELSEAYRVLSREQSRRS 94  
        YYE+LGV  A  E+++A+  + + HPDR+ G+  ++F E+ EAY VL+  Q R +  
Sbjct:   6  YYEILGVSKTAEEREIRKAYKRLAMKYHPDRNQGDKAEAKFKRIKEAYEVLTDSSQKRAA 65  
  
Query:   95 YD 96  
        YD  
Sbjct:   66 YD 67
```


FIGURE 21

>gi|1703590 (U80439) contains similarity to a DNAJ-like domain (Caenorhabditis elegans)
Length = 345

Score = 98 (45.2 bits), Expect = 5.2e-12, Sum P(3) = 5.2e-12
Identities = 17/37 (45%), Positives = 28/37 (75%)

Query: 28 QRSRPSTYYELGVLHPGASTEVEVKRAFFSKSKELHPD 64
++ R T+YE+LGV A+ E+K AF+++SK++HPD
Sbjct: 22 KKIRQRTHYEVLGVESTATLSEIKSAFYAQSKGVHPD 58

Score = 74 (34.1 bits), Expect = 5.2e-12, Sum P(3) = 5.2e-12
Identities = 17/32 (53%), Positives = 19/32 (59%)

Query: 71 SLHSRFVELSEAYRVLSREQSRRSYDDQLRSG 102
S + F+EL AY VL R RR YD QLR G
Sbjct: 64 SATASFLELKNAYDVLRRPADRRLYDYQLRGG 95

Score = 39 (18.0 bits), Expect = 5.2e-12, Sum P(3) = 5.2e-12
Identities = 10/42 (23%), Positives = 19/42 (45%)

Query: 162 LLMLAGMGLHYIAFRKVKQMHILNFMDEKDRITAFYNARAR 203
L+++AG Y+ Q L+ + ++D I F + R
Sbjct: 158 LVLVAGYNGGYLYLLAYNQQLDKLIDEDEIAKCFLRQKEFR 199

>gnl|PID|e281266 (Z81030) C01G10.12 (Caenorhabditis elegans)
Length = 191

Score = 96 (44.3 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
Identities = 17/41 (41%), Positives = 27/41 (65%)

Query: 35 YYELGVLHPGASTEVEVKRAFFSKSKELHPDRDPGNPSLHSR 75
YYE++GV A+ +E++ AF K+K+LHPD+ + SR
Sbjct: 19 YYEIIIGVSASATRQEIRDAFLKTKQLHPDQSRKSSKSDSR 59

Score = 54 (24.9 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
Identities = 10/22 (45%), Positives = 15/22 (68%)

Query: 75 RFVELSEAYRVLSREQSPPSYD 96
+F+ + EAY VL E+ R+ YD
Sbjct: 71 QFMLVKEAYDVLRLTEEKKEYD 92

Score = 35 (16.1 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
Identities = 9/44 (20%), Positives = 22/44 (50%)

Query: 141 QGPQLRQQQHKQKQVLGYCLLLMLAGMGLHYIAFRKVKQMHILN 184
+ P+ + KQ ++L ++A +G + + RK++ L+
Sbjct: 145 RNPEDEYLREKQKNFMLVVLAAATVMALIGANTVYIRKLQADRLS 188

FIGURE 22

>sp|Q10209|YAY1_SCHPO HYPOTHETICAL 44.8 KD PROTEIN C4H3.01 IN CHROMOSOME I
 >gi|1184014 (Z69380) unknown [Schizosaccharomyces pombe]
 Length = 392

Score = 84 (38.8 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
 Identities = 13/35 (36%), Positives = 25/36 (69%)

Query: 35 YYELGVHPGASTEELKRAFFSKSKELHPDRDPGNP 70
 YY+LLG+ A+ ++K+A+ + + HPD++P +P
 Sbjct: 9 YYDLGISTDATAVDIKKAYRKLAVKYHPDKNPDDP 44

Score = 64 (29.5 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
 Identities = 14/40 (35%), Positives = 23/40 (57%)

Query: 75 RFVELSEAYRVLSREQSRRSYDDQLRSGSPKSPRTTVHD 114
 +F ++SEAY+VL E+ R YD + + P+ T +D
 Sbjct: 50 KFQKISEAYQVLGDEKLRSQYDQFGKEAVPEQGFTDAYD 89

Score = 37 (17.1 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
 Identities = 9/29 (31%), Positives = 15/29 (51%)

Query: 190 DRIITAFYNearararanrgilQQERQRL 218
 DR A E A A+ + +++ RQR+
 Sbjct: 149 DRQQAQIREREALAKREQEMIEDRRQRI 177

Score = 33 (15.2 bits), Expect = 0.00081, Sum P(3) = 0.00081
 Identities = 8/19 (42%), Positives = 11/19 (57%)

Query: 140 PQGPQLRQQQHKQNKQVLG 158
 PQG + Q+ + QVLG
 Sbjct: 44 PQGASEKFKISEAYQVLG 62

FIGURE 23

>gnl|PID|e253406 (X77635) tumorous imaginal discs [Drosophila virilis]
 >gnl|PID|e263866 (Y07700) Tid58 protein [Drosophila virilis]
 Length = 529

Score = 153 (70.6 bits), Expect = 9.7e-13, P = 9.7e-13
 Identities = 27/71 (38%), Positives = 44/71 (61%)

Query: 26 AGQSRPSTYYELGVHPGASTEELKRAFFSKSKELHPDRDPGNPSLHRSFVELSEAYRV 85
 + R + YY LGV A+ +++K+A++ +K+ HPD + +P +F ++SEAY V
 Sbjct: 72 SSSRMQAQYYATLGVAQNANAKDIKAYYELAKKYHPDTNKKDQFDASKGQDVSEAYEV 131

Query: 86 LSREQSRRSYD 96
 LS +Q RR YD
 Sbjct: 132 LSDDQKRREYD 142

FIGURE 24

28/32

MCG18	-----MPPLLPLRLCRLWP-RN--PP-----SRLLGAA
HDJ-2	MVKETTYVDVLGVKPNATQEELKKAYRKLALKYHPDKN--PN----EGEZFQKISQAYEV
HDJ-1	MCKD--YYQTLGLARGASDEEIKRAYRRQALRYHPDKNKEPG---AEEKFKEIAEAYDV
HSJ1	M-AS--YYEILDVPRASADDIKKAYRRKALQWHPDKN--PDNKEFAEKKFKEVAEAYEV
.	
MCG18	AGQSRSPSTY--YELLGVIH-----PGA-----ST-EEVKRAFFS--
HDJ-2	LSDAKKRELYDKGGEQAIK-----EGGAGGG-----FGSPMDIFIMFTGGG
HDJ-1	LSDPRKRETFDRYGEGLKGS GP-----SGSGGGANGTSFSTYTFHGDPHAMFAEFTG--
HSJ1	LSDPKRETYDRYGREGLTGTGTGPSRAEAGSGGP--G--FTFT-FKSPPEVTFREFTG--
.	
MCG18	KSKELHPDRDPGNP----SLHSRFVELSEAYRVLREQSRRS--YDQQLRSGSPPKSPRT
HDJ-2	GRMQRRRGKRVVHQLSVTLEDLYNGATRKALQKNVICDKCEGRGGKGAVECCPNCRG
HDJ-1	GRNPFDTFFGQRNGEDGMDIDDPFSGFPKMGQFTNVNFGRS--RSAQEPARKQDPPVT
HSJ1	SGDPFAELFDDLGP--FSELQNRGSRHSGPFFTFSSSFPGHSDFSSSSFSFSGAGAFRS
.	
MCG18	TVHDKSAHQTHSSWTPPNAQY----WSQFHSVRPQ-----GP-----QLRQQQHKON
HDJ-2	TGMQIRIHQIGPMVQQIQSVCMCQGHGERISPK-DRCKSCNGRKIVREKKILEVHIDK
HDJ-1	HDLRVSLEEIYSGCTKQMK-----ISH-KRLNP--D-----GKSIRNEDKILTIEVKK
HSJ1	VSTSTTFVQGRRIITTRIME-----NGQ-ERVEVEED-----GQ-----LKSVTINGVPD
.	
MCG18	KQVLGYCLLL-----MLAGMGLHYIAFRKVKQHLAFMDE-KDRIITAFYNARARARAN
HDJ-2	GMQGGQKITFHGEGDQEPGLEPGDIIIVLDQKDHAVFTRRGEDLFMCMDIQLVEALCGFQ
HDJ-1	GWKEGTXITFPKEGDQTSNNIPADIVFVLKDKPHNIFKRDGSDVIYPARISLREALCGCT
HSJ1	DLARGLELSR-RE--QQP-SVTSRSGGTQVQQTASCPLD-SDLSEDEDLQLAMAYSLSE
.	
MCG18	RGILQQRQRQLQQRQPP-PSEPTQGPPIVPRGAGP-----
HDJ-2	KPISTLDNRTIVITSHPGQIVKHGDIKCVLNEGMPYRRPYEKGRLIIEFKVNFPENGFL
HDJ-1	VNVPTLDGRTIPVVFK--DVIRPGMRKVPGEGLPLPKTPEKRGDLIIEFEVIFPER--I
HSJ1	MEAAGKKPAGGREAQHR-RQGRPRPSTKIQAAGGP--RR--VRG--VKQPNVHPQR-RR
.	
MCG18	-----
HDJ-2	SPDKLSLLEKLLPERKEVEETDEMDQVELVDFDPNQERRRHYNGEAYEDDENHPRGGVQC
HDJ-1	PQTSRTVLEQVLPI-----
HSJ1	PLAASSSEHRAQPD-----LIQILTGGSDSLWEEKRGVS-----
.	
MCG18	---
HDJ-2	QTS
HDJ-1	---
HSJ1	---

* = amino acid identity in all 4 proteins

. = conservative substitution

FIGURE 25

CAAGGAGCCTCTGCCTGCCCGTCGTCGTCATGCCGTCCTGTTGCTCCAGTGCCTCTGC	60
M P S L L L Q L P L	10
GCCTATGCCGGCTGTGGCCGCATAGCCTTTCCATCCGACTTCTCACAGCCGCCACAGGGC	120
R L C R L W P H S L S I R L L T A A T G	30
AGCGGTCTGTCCCTACTAATTACTATGAATTGTTGGGCGTGCATCCGGGTGCCAGCGCTG	180
Q R S V P T N Y Y E L L G V H P G A S A	50
AAGAGATTAAACGTGCTTTTTCACCAAGTCAAAAGAGCTACACCCTGATCGAGACCCTG	240
E E I K R A F F T K S K E L H P D R D P	70
GGAAACCCAGCCCTGCATAGCCGCTTTGTGGAGCTGAATGAGGCATATCGAGTGCTCAGTC	300
G N P A L H S R F V E L N E A Y R V L S	90
GTGAGGAAAGTCGTCGTAACATGACCACCAGCTGCATTACAGCCAGTCCTCCAAAGTCTT	360
R E E S R R N Y D H Q L H S A S P P K S	110
CAGGGAGCACAGCCGAGCCTAAGTATACGCAACAGACACACAGCAGCTCCTGGGAACCCC	420
S G S T A E P K Y T Q Q T H S S S W E P	130
CCAACGCTCAATACTGGGCCCAGTTCACAGTGTGAGGCCGAGGGGCCGGAGTCAAGGA	480
P N A Q Y W A Q F H S V R P Q G P E S R	150
AGCAGCAGCGTAAACACAACCAGCGGGTCTCTGGGGTACTGCCTCCTGCTCATGGTGGCAG	540
K Q Q R K H N Q R V L G Y C L L L M V A	170
GCATGGGCCTGCACTATGTTGCCTTCAGGAAGCTGGAGCAGGTGCATCGCAGCTTCATGG	600
G M G L H Y V A F R K L E Q V H R S F M	190
ATGAAAAGGACCGGATCATTACAGCCATCTACAATGACACTCGGGCCAGGGCCAGGGCCA	660
D E K D R I I T A I Y N D T R A R A R A	210
ACAGAGCCAGGATTCAGCAAGAGCGCCACAGAGGCAGCAGCCTCGGGCAGAACCCCTCCC	720
N R A R I Q Q E R H E R Q Q P R A E P S	230
TGCCTCCAGAAAGCTCCAGGATCATGCCCCAGGACACAAGCCCCTGAGAGGCTTAACTAA	780
L P P E S S R I M P Q D T S P *	245
ATGGGACCTTCATTGGTCTCTCCTGCTGCCTGTCCAGAACTACACGTGCAATAAACTC	840
ATTTTCAG(A) _n	849

FIGURE 26

```

human MCG18      MPPLL---PLRLCRLWPNPPSRLIGAAAGQSRSPSTYYELGLVHPGASTEIVKRAFFSK
mouse MCG18      MPSLLLQLPLRLCRLWPHSLSTRLLTAATQGRSVPTNYELGLVHPGASAEIKRAFFTK
      * * * * *
human MCG18      SKELHPDRDPGNPSLHSRFVELSEAYRVL SREQSRRSYDDQLRSGSPPKSPRTTVHDKSA
mouse MCG18      SKELHPDRDPGNPALHSRFVELNEAYRVL SREESRRNYDHLQHSASP PKSSGSGTAEPKYT
      * * * * *
human MCG18      HQTHSS-WTPPNAQYWSQFHSVRPQGPQLRQQQHKQNKQVLGYCLLLMLAGMGLHYIAFR
mouse MCG18      QQTHSSSWEP PNAQYWAQFHSVRPQGPESRKQQRKHNRQVLGYCLLLMVAGMGLHYVAFR
      * * * * *
human MCG18      KVKQMHLNFMDEKDRIITAFYNEARARARANRGI LQQRQRLQGRQPPSEPTQGPE---
mouse MCG18      KLEQVHRSFMDEKDRIITAIYNDTRARARANRARIQQR---HERQQPRAEPSLPRESSR
      * * * * *
human MCG18      IVPRGAGP
mouse MCG18      IMPQDTSP
      * * *

```

31/32

FIGURE 27

```
ttgaagtctagccccatcctgggtccaatgcgctcttggtagcctcctttccccagctgccc 60
* S L A P S W S N A L L V A S F P S C P

gccccgcgccATGCCGCCCTTACTGCCCCCTGCGCCTGTGCCGGCTGTGCCCCGCAACCC 120
P A A M P P L L P L R L C R L W P R N P>
```

32/32

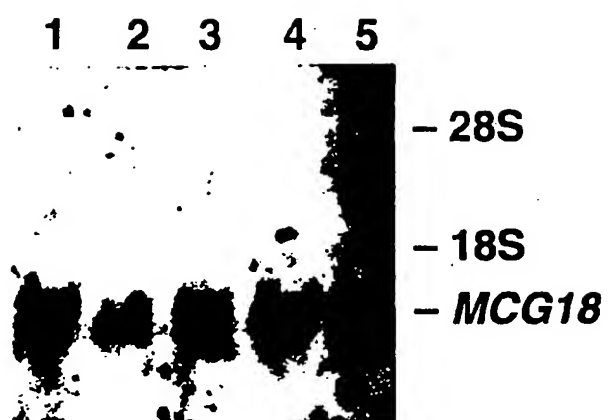
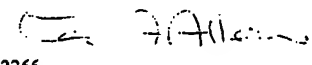


FIGURE 28

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 98/00380

A. CLASSIFICATION OF SUBJECT MATTER		
Int Cl ⁶ : C12N 15/12; C07K 14/47; C07K 16/18; G01N 33/53		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) I/C: WPAT (D gene) Sequences provided by Applicant		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) :EMBL, Genebank, Swiss Prot and PIR: Sequences provided by applicant		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Kedra D, Seroussi E, Fransson I, Trifunovic J, Clark M, Lagercranz J, Blennow E, Mehlin H, Dumanski J, Human Genetics, October 1997 100(5-6) 611-619 The germinal centre kinase gene and a novel CDC25-like gene are located in the vicinity of the PYGM gene on 11q13 EMBL AC Y12339	1-3,8-10,15-18
P,X	Guru S C, Agarwal S K, Manickain P, Olufemi S E, et al Genome Research, July 1997 7(7) 725-735. A transcript map for the 2.8-Mb region containing the multiple endocrine neoplasia type I locus TREMBL AC 014616	1. 4-5, 8, 11-12, 15, 19-21
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/> See patent family annex		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search 16 July 1998		Date of mailing of the international search report 20 JUL 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer GILLIAN ALLEN  Telephone No.: (02) 6283 2266

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 98/00380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 2, 4, 6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
They are to known groups of proteins and lack distinguishing features which would enable a meaningful search.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Invention 1, defined by claims 2, 3, 9, 10, 16-18, is to nucleotide sequences, amino acid sequences and proteins with a zinc finger domain.

Invention 2, defined by claims 4, 5, 11, 12, 19-21, is to nucleotide sequences and amino acid sequences and proteins which are guanine exchange factors.

Invention 3, defined by claims 6, 7, 13, 14, 22-24, is to nucleotide sequences and amino acid sequences and proteins which are heat shock proteins or heat shock binding proteins.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 98/00380

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EMBL AC AF012106 DT 6 November 1997 Lloyd S E and Thakker R V DE Homo Sapiens DnaJ protein (HSPF ₂)mRNA, complete cds	1,6-8,13- 15,22-24
P,X	EMBL AC AF 036875 DT 20 May 1998 Silins G, Grimmond S, Hayward N DE Mus musculus multiple endocrine neoplasia type I candidate protein number 18 mRNA, complete cds	1,6-8,13- 15,22-24

36/85

FIGURE 13(a) (III)

CAA	CAA	TCC	CGG	AAG	GAC	AAC	TCC	AAT	TCC	CTG	CAG	GTG	AAA	ACG	584
Gln	Gln	Ser	Arg	Lys	Asp	Asn	Ser	Asn	Ser	Leu	Gln	Val	Lys	Thr	
180					185					190					
TGC	CAC	CTG	GTC	AGG	TAC	TGG	ATC	TCC	GCC	TTC	CCA	GCG	GAG	TTT	629
Cys	His	Leu	Val	Arg	Tyr	Trp	Ile	Ser	Ala	Phe	Pro	Ala	Glu	Phe	
195					200					205					
GAC	TTG	AAC	CCG	GAG	TTG	GCT	GAG	CAG	ATC	AAG	GAG	CTG	AAG	GCT	674
Asp	Leu	Asn	Pro	Glu	Leu	Ala	Glu	Gln	Ile	Lys	Glu	Leu	Lys	Ala	
210					215					220					
CTG	CTA	GAC	CAA	GAA	GGG	AAC	CGA	CGG	CAC	AGC	AGC	CTA	ATC	GAC	719
Leu	Leu	Asp	Gln	Glu	Gly	Asn	Arg	Arg	His	Ser	Ser	Leu	Ile	Asp	
225					230					235					
ATA	GAC	AGC	GTC	CCT	ACC	TAC	AAG	TGG	AAG	CGG	CAG	GTG	ACT	CAG	764
Ile	Asp	Ser	Val	Pro	Thr	Tyr	Lys	Trp	Lys	Arg	Gln	Val	Thr	Gln	
240					245					250					
CGG	AAC	CCT	GTG	GGA	CAG	AAA	AAG	CGC	AAG	ATG	TCC	CTG	TTG	TTT	809
Arg	Asn	Pro	Val	Gly	Gln	Lys	Lys	Arg	Lys	Met	Ser	Leu	Leu	Phe	
255					260					265					

37/85

FIGURE 13(a) (IV)

GAC CAC CTG GAG CCC	ATG GAG CTG GCG GAG CAT	CTC ACC TAC TTG	854
Asp His Leu Glu Pro	Met Glu Leu Ala Glu His	Leu Thr Tyr Leu	
270	275	280	
GAG TAT CGC TCC TTC	TGC AAG ATC CTG TTT CAG	GAC TAT CAC AGT	899
Glu Tyr Arg Ser Phe	Cys Lys Ile Leu Phe Gln	Asp Tyr His Ser	
285	290	295	
TTC GTG ACT CAT GGC	TGC ACT GTG GAC AAC CCC	GTC CTG GAG CGG	944
Phe Val Thr His Gly	Cys Thr Val Asp Asn Pro	Glu Arg	
300	305	310	
TTC ATC TCC CTC TTC	AAC AGC AGC GTC TCA CAG	TGG GTG CTC ATG	989
Phe Ile Ser Leu Phe	Asn Ser Val Ser Gln Trp	Val Gln Leu Met	
315	320	325	
ATC CTC AGC AAA CCC	ACA GCC CCG CAG CGG	GCC GTC ATC ACA	1034
Ile Leu Ser Lys Pro	Thr Ala Pro Gln Arg	Ile Thr	
330	335	340	

38/85

FIGURE 13(a) (v)

CAC TTT GTC CAC GTG GCG GAG AAG CTG CTA CAG CTG CAG AAC TTC	1079
His Phe Val His Val Ala Val GTC GTC GGC GGC CTG CAG Gln Leu Asn Phe	355
345	
AAC ACG CTG ATG GCA GTG GTC GTC GGC GGC CTG AGC CAC AGC TCC ATC	1124
Asn Thr Leu Met Ala Val Val Val GTC GTC GGC GGC CTG AGC CAC AGC TCC ATC	370
360	
TCC CGC CTC AAG GAG ACC CAC AGC AGC GTC AGC CCT GAG ACC ATC	1169
Ser Arg Leu Lys Lys Glu Thr Thr His Ser His Val Ser Pro Glu Thr Ile	385
375	
AAG CTC TGG GAG GGT CTC ACG GAA CTA GTG ACG GCG ACA GGC AAC	1214
Lys Leu Trp Glu Gly Leu Thr Thr Thr Val Thr Ala Thr Gly Asn	400
390	
TAT GGC AAC TAC CGG CGT CGG CTG GCA GCC TGT GTG GGC TTC CGC	1259
Tyr Gly Asn Tyr Arg Arg Arg Thr Thr Thr Thr Thr Cys Val Gly Phe Arg	415
405	
TTC CCG ATC CTG GGT GTG CAC CTC AAG GAC CTG GTG GCC CTG CAG	1304
Phe Pro Ile Leu Gly Val Val His Leu Lys Asp Leu Val Ala Leu Gln	430
420	

39/85

FIGURE 13(a) (VI)

CTG GCA CTG CCT GAC	TGG CTG GAC CCA GCC CGG ACC CGG CTC AAC	1349
Leu Ala Leu Pro Asp	Leu Asp Pro Ala Arg Thr Arg Leu Asn	
435	440	445
GGG GCC AAG ATG AAG CAG	CTC TTT AGC ATC CTG GAG GAG CTG GCC	1394
Gly Ala Lys Met Lys	Leu Phe Ser Ile Leu Glu Glu Leu Ala	
450	455	460
ATG GTG ACC AGC CTG CGG CCA CCA GTA CAG GCC AAC CCC GAC CTG		1439
Met Val Thr Ser Leu	Pro Arg Pro Val Gln Ala Asn Pro Asp Leu	
465	470	475
CTG AGC CTG CTC ACG CTG GTG	TCT CTG GAT CAG TAT CAG ACC GAG GAT	1484
Leu Ser Leu Leu Thr	Val Ser Leu Asp Gln Tyr Thr Glu Asp	
480	485	490
GAG CTG TAC CAG CTG TCC CTG CAG CGG GAG CCG CGC TCC AAG TCC		1529
Glu Leu Tyr Gln Leu	Leu Ser Leu Gln Arg Glu Pro Arg Ser Lys Ser	
495	500	505

40/85

FIGURE 13(a) (VII)

TCG CCA ACC AGC CCC	ACG AGT TGC ACC CCA CCA CCC CGG CCC CCG	1574
Ser Pro Thr Ser Pro	Pro Pro Pro Arg Pro Pro	
510	520	
GTA CTG GAG GAG TGG ACC TCG GCT GCC AAA CCC AAG CTG GAT CAG	1619	
Val Leu Glu Glu Trp Thr Ser Ala Ala Lys Pro Lys Leu Asp Gln		
525	535	
GCC CTC GTG GTG GAG CAC ATC GAG AAG ATG GTG GAG TCT GTG TTC	1664	
Ala Leu Val Val Glu His Ile Glu Lys Met Val Glu Ser Val Phe		
540	550	
CGG AAC TTT GAC GTC GAT GGG GAT GGC CAC ATC TCA CAG GAA GAA	1709	
Arg Asn Phe Asp Val Asp Gly Asp Gly His Ile Ser Gln Glu Glu		
555	565	
TTC CAG ATC ATC CGT GGG AAC TTC CCT TAC CTC AGC GCC TTT GGG	1754	
Phe Gln Ile Ile Arg Gly Asn Phe Pro Tyr Leu Ser Ala Phe Gly		
570	580	
GAC CTC GAC CAG AAC CAG GAT GGC TGC ATC AGC AGG GAG GAG ATG	1799	
Asp Leu Asp Gln Asn Gln Asp Gly Cys Ile Ser Arg Glu Glu Met		
585	595	

41/85

FIGURE 13(a) (VIII)

GTT	TCC	TAT	TTC	CTG	CGC	TCC	AGC	TCT	GTG	TTG	GGG	GGG	CGC	ATG	1844
Val	Ser	Tyr	Phe	Leu	Arg	Ser	Ser	Ser	Val	Leu	Gly	Gly	Arg	Met	
600					605					610					
GGC	TTC	GTA	CAC	AAC	TTC	CAG	GAG	AGC	AAC	TCC	TTG	CGC	CCC	GTC	1889
Gly	Phe	Val	His	Asn	Phe	Gln	Glu	Ser	Asn	Ser	Leu	Arg	Pro	Val	
615					620					625					
GCC	TGC	CGC	CAC	TGC	AAA	GCC	CTG	ATC	CTG	GGC	ATC	TAC	AAG	CAG	1934
Ala	Cys	Arg	His	Cys	Lys	Ala	Leu	Ile	Leu	Gly	Ile	Tyr	Lys	Gln	
630					635					640					
GGC	CTC	AAA	TGC	CGA	GCC	TGT	GGA	GTG	AAC	TGC	CAC	AAG	CAG	TGC	1979
Gly	Leu	Lys	Cys	Arg	Ala	Cys	Gly	Val	Asn	Cys	His	Lys	Gln	Cys	
645					650					655					
AAG	GAT	CGC	CTG	TCA	GTT	GAG	TGT	CGG	CGC	AGG	GCC	CAG	AGT	GTG	2024
Lys	Asp	Arg	Leu	Ser	Val	Glu	Cys	Arg	Arg	Arg	Ala	Gln	Ser	Val	
660					665					670					

42/85

FIGURE 13(a) (IX)

AGC CTG GAG GGG TCT	GCA CCC TCA CCC ATG CAC AGC CAC	2069
Ser Leu Glu Gly Ser	Pro Met His Ser His	
675	685	
CAT CAC CGC GCC TTC AGC TTC TCT CTG CCC CGC CCT GGC AGG CGA	2114	
His His Arg Ala Phe Ser Phe Ser Leu Pro Arg Pro Gly Arg Arg		
690	700	
GGC TCC AGG CCT CCA GAG ATC CGT GAG GAG GTA CAG ACG GTG	2159	
Gly Ser Arg Pro Pro Glu Ile Arg Glu Glu Val Gln Thr Val		
705	715	
GAG GAT GGG GTG TTT GAC ATC CAC TTG TA ATAGATGCTG	2198	
Glu Asp Gly Val Phe Asp Ile His Leu *		
720	725	
TGGTTGGATC AAGGACTCAT TCCTGCCCTG GAGAAATAC TTCAACCAGA	2248	
GCAGGGAGCC TGGGGGTGTC GGGGCAGGAG GCTGGGGATG GGGGTGGGAT	2293	
ATGAGGGTGG CATGCAGCTG AGGCAGGGC CAGGGCTGGT GTCCCTAAGG	2348	

43/85

FIGURE 13(a) (X)

TTGTACAGAC TCTTGTGAAT ATTTGTATTT TCCAGATGGA ATAAAAAGGC	2398
CCGTGTAATT AACCTTC (A)n	2416

44/85

FIGURE 13 (b)

CGATTTCATT CCTCGCTCCC CACAGGTCCC TCTCCCCAAA ATATTCCCAT	50
CTTGTCCTAG CCATATCCCC AGACTATCTC AAGGACCAGC TGTCCCCACG	100
CCCCCGACCT CCACTAGGCC TGTGCCACCC GCTGCCCTGCA GGAAGACGCC	150
CGGTCCCCGG CCGGGTTAG CCC CAT GGG AAC GGG GTT CGG TCC GAG	196

* Pro His Gly Asn Gly Val Arg Ser Glu

1	5
CCC GGT GGG AGG CTC CCG GAG CGC AGC CTG GGC CCA GCC CAC	238
Pro Gly Gly Arg Leu Pro Glu Arg Ser Leu Gly Pro Ala His	
10	20
CCC GCG CCG GCG GCC <u>ATG</u> GCA GGC ACC CTG GAC CTG GAC AAG	280
Pro Ala Pro Ala Ala Met Ala Gly Thr Leu Asp Leu Asp Lys	
25	30
GGC TGC ACG GTG GAG GAG CT	300
Gly Cys Thr Val Glu Glu Leu	
40	35

45/85

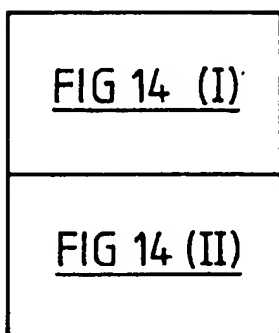


FIG 14

46/85

FIGURE 14 (I)

1	MAGTLDDKGC...TVEELLRGCI EAF..DDSGKV RDPQLVRMFLMMHPW	45
1	MSSKVEEDQH QELLTEDQLVARC VECFDVDEEDED EDEIEFVDALFLSHQW	50
46	YIPSSQLAAKLLHIYQQSRKDNSNSLQVKTCHLVRYWISAFPAEFDLNPE	95
51	LSDSLSLITHFVNFYQETRNVEQRE...AVCRAVSFWIEKFFPMHFDAQPQ	97
96	LAEQIKELKALLDQEGNRRHSSLIDIDSVPPTYKWK RQVTQRNPVGQKK..	143
98	VCAQVVRLKTI AEDINENIRNGL.DVSALP SFAWLRAVSVRNPLAKQTIV	146
144RKMSLLFDHLEPMELAEHLTYLEYR	168
147	RVDFETLPTPGTPPPFPPIASKKFSLTAFSLSFVQASPSDISTLSLHIDYR	196
169	SFCKILFQDYHSFVTHGCTVDNPVLERFISL FNSVSQWVQLMILSKPTAP	218
197	VLSTISITELKQYVKDGHRLRSCPMLE RSI SVFN NLSNWVQCLILNKTTPK	246
219	QRALVITHEVHVAEKLLOLONENTLMAVVGGLSHSSISR LKETSHVSP E	268
247	ERAEILVKFVHVAKHLRKINNFENTLMSVVGGIT HSSVARLAKTYAVLSND	296
269	TIKLWEGLTELVTATGNYGN YRRRLAAC.VGFRFPILGVHLKDLVALQLA	317
297	IKKELTQLTNLLSAQHNFCEYRKALGACNKKFRIP IIGVHLKDLVAINCS	346

47/85

FIGURE 14 (II)

318	LPDWLDPARTRLNGAKMKQLFSILEELAMVTSLRPPV.QANPDLLSLLTV	366
347	GANFEKT..KCISSDKLVKLSKLLSNFLVFNQKGHNLPENMDLINTLKV	394
367	SLDQYQTEDELYQLSLQREPRSKSSPTSCTPPPRPPVLEEWTSAAKP	416
395	SLDIRYNDDDIYELSLRREP KTFMN.....FEPSRGLVFAEWASGVTV	437
417	KLDQALVVEHIEKMVESVFRNFDVDGDGHIISOEEFQIIRGNFPYLSAFGD	466
438	APDNATVSKHISAMVDAVFKHYDHD RDGFIISOEEFQIAGNFPFIDAFVN	487
467	L DONODGCISREEMVSYFLRSS.SVLGGRMGFVHNFOESNSLRPVACRHC	515
488	IDVDM DGOISKDELKTYFMAANKNTKDLRRGFKHNFHETTELPTTCNHC	537
516	KALLIGLYKOGCLKRACGVNCHKOCKDRLSVECRRRRAQSVSLEGSA PPS	565
538	NKLLWGILROGEKCKDCGLAVHSCCKSNVAECRRKSSSNLTRA AEW FAS	587
566	PMHSHHHRAFSFSLPRPGRRGSRPPPEIREEEVQTVEDGVFDIHL	609
588	PRGSMRSRIINTC...NNSGSTPDEEIGLVSLACEEVFEDDDL	627

48/85

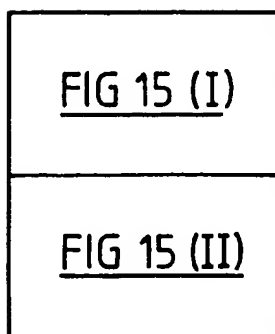


FIG 15

FIGURE 15 (I)

human CGATTTCATT CCTCGCTCCC CACAGGTCCC TCTCCCCAAA ATATTCCCAT CTTGTCCCTAG 60
human CCCATCCCCC AGACTATCTC AAGGACCAGC TGTCCCCACG CCCCCGACCT CCACTAGGCC 120
human TGTGCCACCC GCTGCCCTGCA GGAAGACGCC CCGTCCCCGG CCGGTTAGC CCCATGGGAA 180
human CGCAGCGCCT GTGTGGCCGC GGGACTCAAG GCTGGCCTGG CTCAAGTGAA CAGCACGTCC 240
mouse ***tcag** ***ag**** t***** ***a*g***t>
human AGGAGGCGAC CTCGTCCGCG GGTTCGATT CTGGGTGGA CGAGCTGGG GTTCGGTCCG 300

acagg

49/85

mouse g*****t**a **-*catt** ***** **aa**aa* g**ct***** **a**aat**>
human AGCCCGGTGG GAGGCTCCCG GAGCGCAGCC TGGGCCCAGC CCACCCCGCG CCGCGGCCA 360
mouse ***a*t**** *****tga ***t*t*a*t ***t*t*** ***-tg**a *****>
human TGGCAGGCAC CCTGGACCTG GACAAGGCT GCACGGTGGA GGAGCTGCTC CGCGGGTGCA 420
mouse ***ga**** t*****t* *****t* ****c**** *****t**t**c**t**>
human TCGAAGCCTT CGATGACTCC GGAAGGTGC GGGACCCGCA GCTGGTGCGC ATGTTCTCTCA 480

FIGURE 15 (II)

```

mouse ***** t*****t *****t***>
human TGATGCACCC CTGGTACATC CCTCCTCTC AGCTGGCGGC CAAGCTGCTC CACATCTACC 540
mouse *****t*****a *****tt* g**a*****t***>
human AACAAATCCCG GAAGGACAAC TCCAATTCCC TGCAGGTGAA AACGTGCCAC CTGGTCAGGT 600
mouse *g*****t*****t* *a***a*****t*****t***>
human ACTGGATCTC CGCCTTCCCA GCGGAGTTTG ACTTGAACCC GGAGTTGGCT GAGCAGATCA 660
mouse *****a*****a*****c* *****a*****c*****>
human AGGAGCTGAA GGCTCTGCTA GACCAAGAAG GGAACCGACG GCACAGCAGC CTAATCGACA 720
mouse *****t** *****ca* *****>
human TAGACAGCGT
mouse *c**g**t**

```

730

51/85

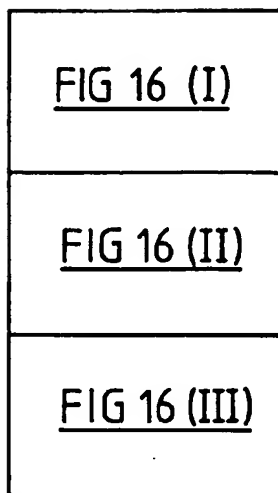


FIG 16

52/85

FIGURE 16 (I)

CACGCCCTCGG	AAGGAGGTT	TGGGGTCGGT	GGTTACACAG	TGAGTGTGTC	50
TGAAGCCAAA	TGGTCGAAA	CCGTTACCCG	CTCTCCTAG	GCC CGG CTA	98
				* Ala Arg Leu	
GTG GGG ACC CCA ACC GCC	TGC GGC	TGC TCC	CAA GTT	CCT	140
Val Gly Thr Pro Thr Ala Cys Gly	Cys Pro Ser	Gln Val	Pro		
	10	15			
CCC TGT TGG CCA GGC ATC	CAG GTC	TCC AGT	CTC CGA	GCT GCG	182
Pro Cys Trp Pro Gly Ile Gln Val	Ser Ser	Leu Arg	Ala Ala		
	20	25	30		
GAG AAC CCA CCG CCA CAT	GCG GCT	GCC CCT	TTC CAT	TCG ACC	224
Glu Asn Pro Pro Pro His Ala Ala	Ala Ala	Pro Phe	His Ser	Thr	
	35	40	45		
CTG TGG GGA GCC AGG	CTT CCG	GGG CCC	CGT TCC	TCC TGT	266
Leu Trp Gly Ala Arg	Leu Pro Gly	Pro Arg	Ser Ser	Cys Val	
	50	55			
AAC TGG GCC CCC CGC	CCC CAT	TCC CAG	ACA TCA	AGG CCG	308
Asn Trp Ala Pro Arg	Pro His Ser	Gln Thr	Ser Arg	Pro Arg	
	60	65	70		

53/85

FIGURE 16 (II)

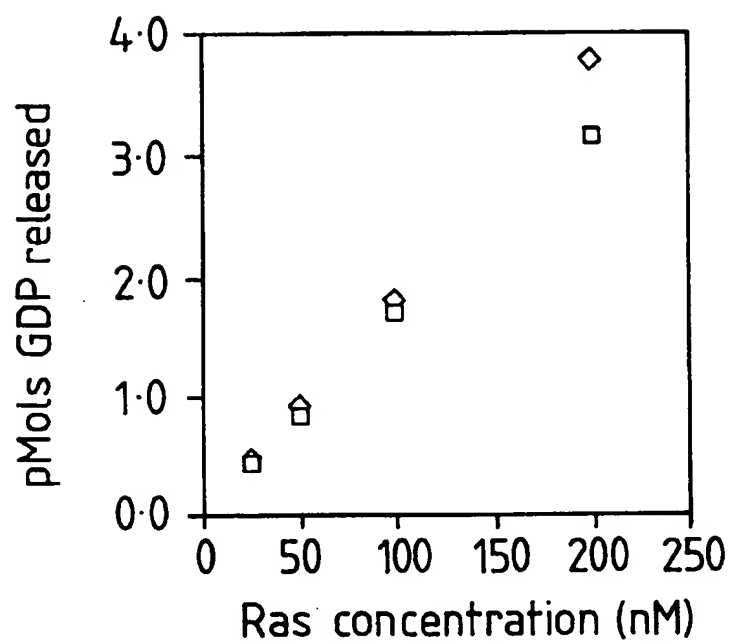
CTC CAG ATA GCC	ACG ATT TCA TTC CTC	GCT GCT CCC CAC	AGG TCC	350
Leu Gln Ile Ala	Thr Ile Ser Phe	Leu Ala Pro His	Arg Ser	
75	80	85		
CTC TCC CCA AAA	TAT TCC CAT CTT GTC	CTA GCC CAT CCC	CCA	392
Leu Ser Pro Lys	Tyr Ser His Leu	Val Leu Ala His	Pro Pro	
90	95	100		
GAC TAT CTC AAG	GAC CTG TCC CCA CGC	CCC CGA CCT	CCA	434
Asp Tyr Leu Lys	Asp Gln Leu Ser	Pro Arg Pro Pro	Pro	
105	110	115		
CTA GGC CTG TGC	CAC CCG CTG CCT GCA	GGA AGA CGC	GTC	476
Leu Gly Leu Cys	His Pro Leu Pro	Gly Arg Arg Pro	Val	
120	125			
CCG GGC CGG GTT	AGC * AGC GGA ACG	CAG CGC CTG TGT	GGC	518
Pro Gly Arg Val	Ser Pro Met Gly	Thr Gln Arg Leu	Cys Gly	
130	135	140		

54/85

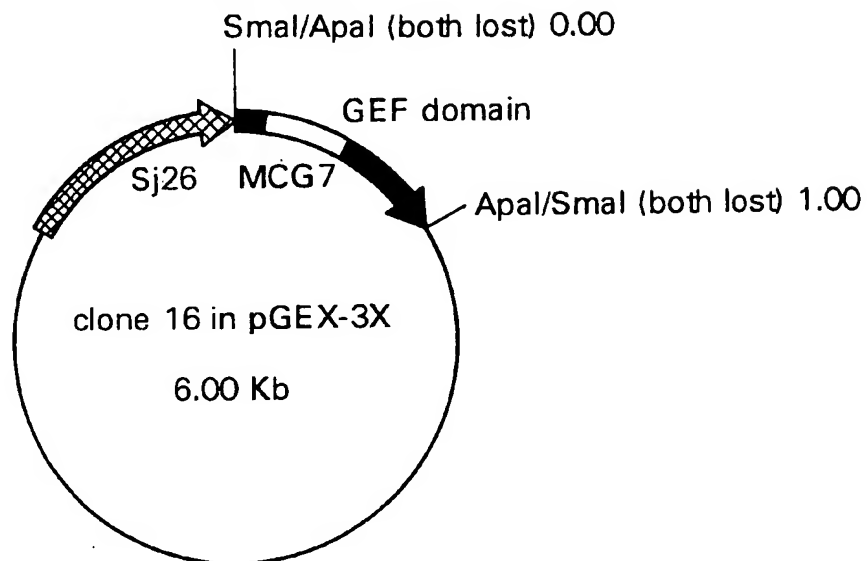
FIGURE 16 (III)

CGC GGG ACT CAA GGC TGG CCT GGC TCA AGT GAA CAG CAC GTC	560
Arg Gly Thr Gln Gly Trp Pro Gly Ser Ser Glu Gln His Val	
145	
150	
155	
CAG GAG GCG ACC TCG TCC TCG GGT TTG CAT TCT GGG GTG GAC	602
Gln Glu Ala Thr Ser Ser Ala Gly Leu His Ser Gly Val Asp	
155	
160	
165	
GAG CTG GGG GTT CGG TCC GAG CCC GGT GGG AGG CTC CCG GAG	644
Glu Leu Gly Val Arg Ser Glu Pro Gly Gly Arg Leu Pro Glu	
170	
175	
180	
CGC AGC CTG GGC CCA GCC CAC CCC GCG CCG GCG GCC ATG GCA	686
Arg Ser Leu Gly Pro Ala His Pro Ala Pro Ala Met Ala	
185	
190	
GGC ACC CTG GAC CTG GAC GAG GGC TGC ACG GTG G	720
Gly Thr Leu Asp Leu Asp Lys Gly Cys Thr Val	
195	
200	
205	

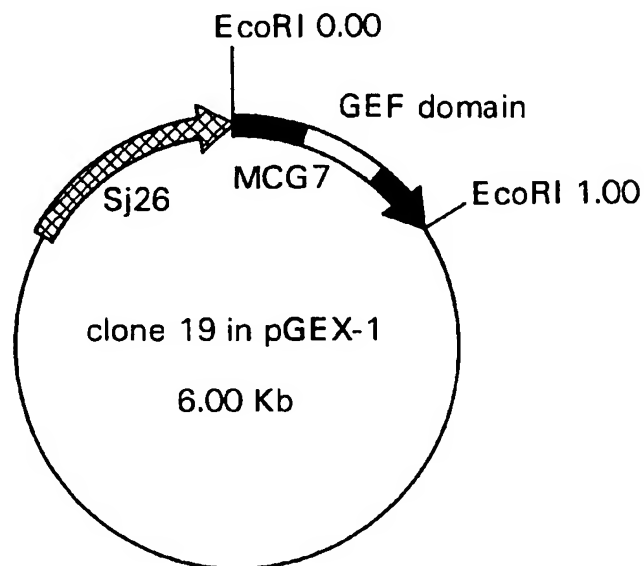
55/85

FIGURE 17

56/85

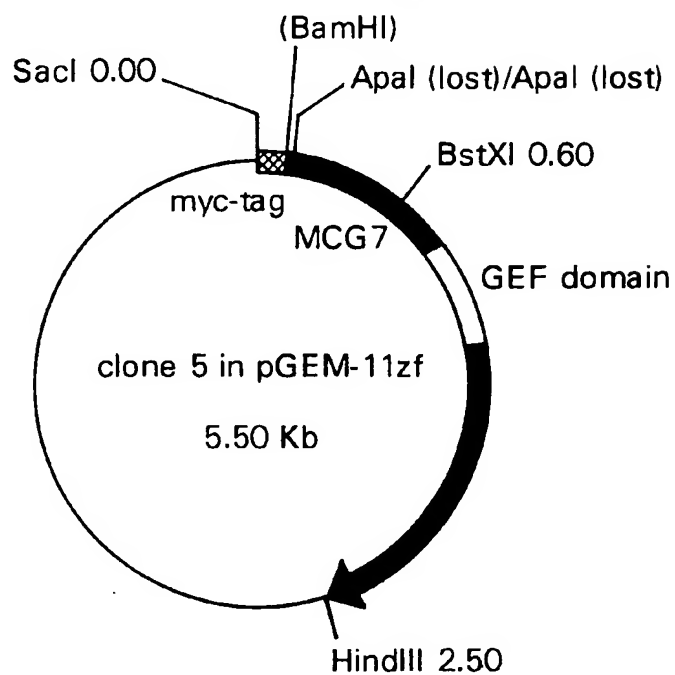
FIGURE 18 (Cont. I)

Plasmid name: clone 16 in pGEX-3X
Plasmid size: 6.00 kb

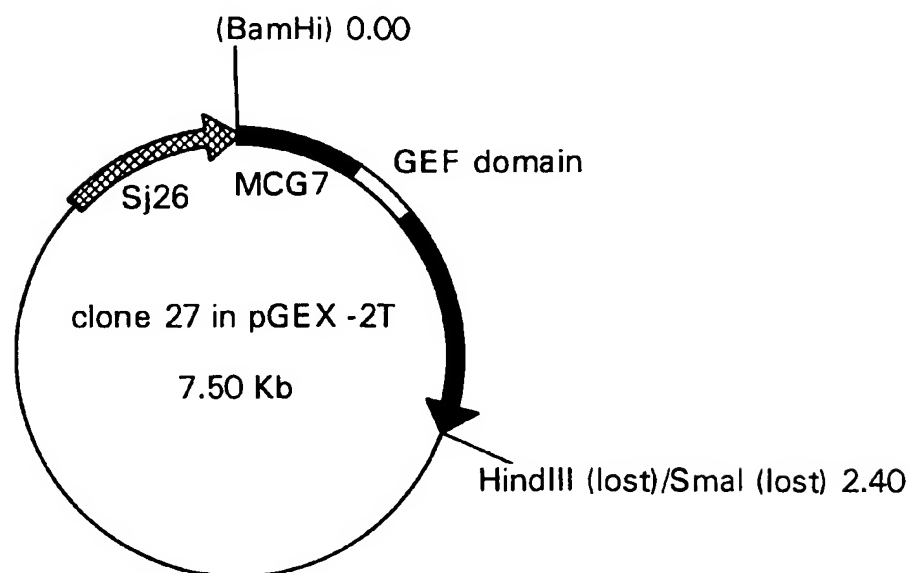
FIGURE 18 (Cont. II)

Plasmid name: clone 19 in pGEX-1
Plasmid size: 6.00 Kb

57/85

FIGURE 18 (Cont. III)

Plasmid name: clone 5 in pGEM-11zf
Plasmid size: 5.50 kb



Plasmid name: clone 27 in pGEX-2T
Plasmid size: 7.50 kb

FIGURE 18 (Cont. IV)

SUBSTITUTE SHEET (RULE 26)

58/85

<u>FIG 19 (I)</u>
<u>FIG 19 (II)</u>
<u>FIG 19 (III)</u>
<u>FIG 19 (IV)</u>

FIG 19

59/85

FIGURE 19 (I)	
GCCCGCCGCC ATG CCG CCC TTA CTG CCC CTG CGC CTG TGC CGG	43
Met Pro Pro Leu Leu Pro Leu Arg Leu Cys Arg	10
1	5
CTG TGG CCC CAG CGG AAC CCT CCC TCC CGG CTC CTC GGA GCG GCC	85
Leu Trp Pro Arg Asn Pro Pro Ser Arg Leu Leu Gly Ala Ala	25
15	20
GCC GGG CAG CGG TCC AGA CCC AGT ACT TAT TAT GAA CTG TTG	127
Ala Gly Gln Arg Ser Arg Pro Ser Thr Tyr Tyr Glu Leu Leu	35
30	35
GGG GTG CAT CCT GGT GCC AGC ACT GAG GAA GTT AAA CGA GCT	169
Gly Val His Pro Gly Ala Ser Thr Glu Glu Val Lys Arg Ala	50
40	45
TTC TTC TCC AAG TCC TCC AAA GAG CTG CAC CCA GAC CGG GAC CCT	211
Phe Phe Ser Lys Ser Lys Glu Leu His Pro Asp Arg Asp Pro	60
55	65
GGG AAC CCA AGC CTG CAC AGC CGC TTT GTG GAG CTG AGC GAG	253
Gly Asn Pro Ser Leu Leu His Ser Arg Phe Val Glu Leu Ser Glu	75
70	80

60/85

FIGURE 19 (II)															295
GCA	TAC	CGT	GTG	CTC	AGC	CGT	GAG	CAG	AGC	CGC	CGC	AGC	AGC	TAT	
Ala	Tyr	Arg	Val	Leu	Ser	Arg	Glu	Gln	Ser	Arg	Arg	Ser	Ser	Tyr	95
85															90
GAT	GAC	CAG	CTC	CGC	TCA	GGT	AGT	CCC	CCA	AAG	TCT	CCA	CGA		337
Asp	Asp	Gln	Leu	Arg	Ser	Gly	Ser	Pro	Pro	Lys	Ser	Pro	Arg		
100															105
ACC	ACA	GTC	CAT	GAC	AAG	TCT	GCC	CAC	CAA	ACA	CAC	AGC	TCC		379
Thr	Thr	Val	His	Asp	Lys	Ser	Ala	His	Gln	Thr	His	Ser	Ser		
110															115
TGG	ACA	CCC	CCC	AAC	GCA	CAG	TAC	TGG	TCC	CAG	TTT	CAC	AGC		421
Trp	Thr	Pro	Pro	Asn	Ala	Gln	Tyr	Trp	Ser	Gln	Phe	His	Ser		
125															130
GTG	AGG	CCA	CAG	GGG	CCC	CAG	TTG	AGG	CAG	CAG	CAA	CAC	AAA		463
Val	Arg	Pro	Gln	Gly	Pro	Gln	Leu	Arg	Gln	Gln	Gln	His	Lys		
140															145
CAA	AAC	AAA	CAA	GTG	CTG	GGG	TAC	TGC	CTC	CTC	CTC	ATG	CTG		505
Gln	Asn	Lys	Gln	Val	Leu	Gly	Tyr	Cys	Leu	Leu	Leu	Met	Leu		
155															160
															165

61/85

FIGURE 19 (III)

GCG GGC ATG GGC	CTG CAC TAC ATT GCC TTC AGG AAG GTG AAG	547
Ala Gly Met Gly	Leu Tyr Ile Ala Phe Arg Lys Val Lys	
	170 175	
CAG ATG CAC CTT AAC	TTC ATG GAT GAA AAG GAT CGG ATC ATC	589
Gln Met His Leu Asn	Phe Met Asp Glu Lys Asp Arg Ile Ile	
180 185	190	
ACA GCC TTC TAC AAC GAA GCC CGG GCA CGG GCC AGG GCC AAC		631
Thr Ala Phe Tyr Asn Glu Ala Arg Ala Arg Ala Asn		
195 200	205	
AGA GGC ATC CTT CAG CAG GAG CGA CAA CGG CTA GGG CAG CGG		673
Arg Gly Ile Leu Gln Gln Gln Arg Gln Arg Leu Gly Gln Arg		
210 215	220	
CAG CCG CCA CCA TCC GAG CCA ACC CAA GGC CCC GAG ATC GTG		715
Gln Pro Pro Pro Ser Glu Glu Pro Thr Gln Gln Gly Pro Glu Ile Val		
225 230	235	
CCC CGG GGC GCC GGC CCC TGA GGGGCTC ACCTGGATGG GGCCTGCAGT		763
Pro Arg Gly Ala Gly Pro	*	
	240	

62/85

FIGURE 19 (IV)
GCGTCCCGC TTTGCTTCCT TCCCTGGACG GCCCGCTCCC CGAAACGCCG 813
GCAATAAAGT GATTCGCAG 832

FIGURE 20

>sp|P08622|DNAJ_ECOLI DNAJ PROTEIN >pir ||HHECDJ heat shock protein
dnaJ -

Escherichia coli >gi |145769 (M12565)-heat shock protein dnaJ
[Escherichia coli] >gi |216441 (D10483) dnaJ protein
[Escherichia coli]

Length = 376

Score = 138 (63.7 bits), Expect = 1.2e-10, P = 1.2e-10

Identities = 25/62 (40%), Positives = 39/62 (62%)

63/85

Query: 35 YYELLGVHPGASTEVEVKRAFFSKSKELHPDRDPGNPSLHSRFVELSEAYRVLSREQSRRS94

YYE+LGV A E+++A+ + + HPDR+ G+ ++F E+ EAY VL+ Q R +

Sbjct: 6 YYEILGVSKTAEEREIRKAYKRLAMKYHPDRNQGDKEAEAKFKEIKEYEVLTDQSQRRAA65

Query: 95 YD 96

YD

Sbjct: 66 YD 67

64/85

<u>FIG 21 (I)</u>
<u>FIG 21 (II)</u>
<u>FIG 21 (III)</u>
<u>FIG 21 (IV)</u>

FIG 21

65/85

FIGURE 21 (I)

>gi|1703590 (U80439) contains similarity to a DNAJ-like domain
(Caenorhabditis elegans]

Length = 345

Score = 98 (45.2 bits), Expect = 5.2e-12, Sum P(3) = 5.2e-12
Identities = 17/37 (45%), Positives = 28/37 (75%)

Query: 28 QRSRPSTYYELLGVHPGASTE EVKRAFFSKSKELHPD 64

++ R T+YE+LGV A+ E+K AF+++SK++HPD

Sbjct: 22 KKIRQRTHEYVLGVESTATLSEIKSAFYAQSKKVHPD 58

Score = 74 (34.1 bits), Expect: = 5.2e-12, Sum P(3) = 5.2e-12
Identities = 17/32 (53%), Positives = 19/32 (59%)

FIGURE 21 (II)

Query: 71 SLHSRFVELSEAYRVLSREQSRRSYDDQLRSG 102

S + F+EL AY VL R RR YD QLR G

Sbjct: 64 SATASFLELKNAYDVLRPPADRRRLYDYQLRGG 95

Score = 39 (18.0 bits), Expect = $5.2e-12$, Sum P(3) = $5.2e-12$
 Identities = 10/42 (23%), Positives = 19/42 (45%)

66/85

Query: 162 LLMLAGMGLHYIAFRKVKQMHLNFMDEKDRIITAFYNEARAR 203

L+++AG Y+ Q L+ + ++D I F + R

Sbjct: 158 LVLVAGYNGGYLLLAYNQQLDKLIDEDEIAKCFLRQKEFR 199

67/85

FIGURE 21 (III)

>gnl |PID |e281266 (Z81030) COLG10.12 [Caenorhabditis elegans]

Length = 191

Score = 96 (44.3 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
Identities = 17/41 (41%), Positives = 27/41 (65%)

Query: 35 YYELLGVHPGASTE EVKRAFFSKSKELHPDRDPCNP SLHSR 75

YYE++GV A+ +E++ AF K+K+LHPD+ + SR

Sbjct: 19 YYEIIGVSASATRQEIRDAFLKKTQQLHPDQSRKSSKSDSR 59

Score = 54 (24.9 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
Identities = 10/22 (45%), Positives = 15/22 (68%)

Query: 75 RFVELSEAYRVLRSREQSRRSYD 96

+F+ + EAY VL E+ R+ YD

68/85

FIGURE 21 (IV)

Sbjct: 71 QFMLVKEAYDVLNRNEEKREYD 92

Score = 35 (16.1 bits), Expect = 1.8e-09, Sum P(3) = 1.8e-09
 Identities = 9/44 (20%), Positives = 22/44 (50%)

Query: 141 QGPQLRQQQHKQNKQVLGYCLLLMLAGMGLHYIAFRKVKQMHLN 184

+ P+ + KQ ++L ++A +G + + RK++ L+

Sbjct: 145 RNPEDEYLREKQKNRMLVVLAAATVMALIGANIVYIRKLQADRLS 188

69/85

FIG 22 (I)

FIG 22 (II)

FIG 22 (III)

FIG 22

70/85

FIGURE 22 (I)

>sp|Q10209|YAY1_SCHPO HYPOTHETICAL 44.8 KD PROTEIN C4H3.01 IN
 CHROMOSOME I
 >gi|1184014 (Z69380) unknown [Schizosaccharomyces pombe]
 Length = 392

Score = 84 (38.8 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
 Identities = 13/36 (36%), Positives = 25/36 (69%)

Query: 35 YYELLGVHPGASTE EVKRAFFSKSKELHPDRDPGNP 70

YY+LLG+ A+ ++K+A+ + + HPD++P +P

Sbjct: 9 YYDLLGISTDATAVDIKKAYRKLAVKYHPDKNPDDP 44

Score = 64 (29.5 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
 Identities = 14/40 (35%), Positives = 23/40 (57%)

71/85

FIGURE 22 (II)

Query: 75 RFVELSEAYRVLSREQRRSYDDQLRSGSPKSPRTTVHD 114

+F ++SEAY+VL E+ R YD + + P+ T +D

Sbjct: 50 KFQKISEAYQVLGDEKLLRSQYDQFGKEKAVPEQGFTDAYD 89

Score = 37 (17.1 bits), Expect = 4.1e-08, Sum P(3) = 4.1e-08
Identities = 9/29 (31%), Positives = 15/29 (51%)

Query: 190 DRIITAFYNEARARARANRGILQQERQRL 218

DR A E A A+ + +++ RQR+

Sbjct: 149 DRKKNAQIREREALAKREQEMIEDRRQRI 177

Score = 33 (15.2 bits), Expect = 0.00081, Sum P(3) = 0.00081

Identities = 8/19 (42%), Positives = 11/19 (57%)

72/85

FIGURE 22 (III)

Query: 140 PQGPQLRQQQHKQNKQVLG 158

PQG + Q+ + QVLG

Sbjct: 44 PQGASEKFQKISEAYQVLG 62

FIGURE 23

>gnl|PID|e253406 (X77635) tumorous imaginal discs [Drosophila virilis]
 >gnl|PID|e263866 (Y07700) Tid58 protein [Drosophila virilis]
 Length = 529

Score = 153 (70.6 bits), Expect = 9.7e-13, P = 9.7e-13
 Identities = 27/71 (38%), Positives = 44/71 (61%)

73/85

Query: 26

AGQSRPSTYYELLGVHPGASTEVEVKRAFFSKSKELHPDRDPGNPSLHSRFFVELSEAYRV 85
 + R + YY LGV A+ +++K+A++ +K+ HPD + +P +F ++SEAY V

Sbjct: 72

SSSRMQAKDYATLGVAKNANAKDIKKAYYELAKKYHPDTNKDDPDASKKFQDVSEAYEV 131

Query: 86 LSREQSRRSYD 96

LS +Q RR YD

Sbjct:132 LSDDQKRREYD 142

74/85

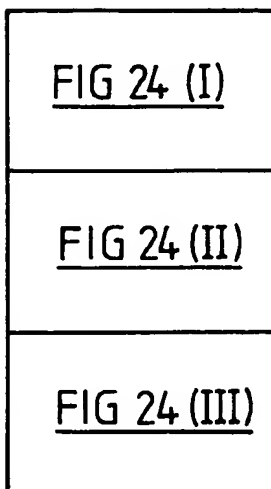


FIG 24

MCG18	-----MPPLPLRLCRLWP-RN--PP-----SRLLGAA
HDJ-2	MVKETYYDVLGVKPNATQEELKKAYRKLALKYHPDN--PN-----EGEKFKQISQAYEV
HDJ-1	MGKD--YYQTLGLARGASDEEIKRAYRRQALRYHPDNKEPG---AEEKFKEIAEAYDV
HSJ1	M-AS--YYEILDVPRASADDIKKAYRRKALQWHPDN--PDNKEFAEKKFKEVAEAYEV . * . * *
MCG18	AGQSRPSTY--YELLGVBH-----PGA-----ST-EEVKRAFFS-
HDJ-2	LSDAKKRELYDKGGEQAIAK-----EGGAGG-----FGSPMDIFDMFFGGG
HDJ-1	LSDPRKREIFDRYGEGLKGSGP-----SGSGGGGANGTSFSYTFHGDPHAMFAEFFG--
HSJ1	LSDKHKREIYDRYGREGLTGTGTGPSRAEAGSGGP--G--FTFT-FRSPEEVFREFFG-- . . . * *
MCG18	KSKELHPDRDPGNP-----SLHSRFVELSEAYRVLSTREQSRRS--YDDQLRSGSPPKSPRT
HDJ-2	GRMQRERRGKNVVHQLSVTLEDLYNGATRKLALQKNVICDKCEGRGGKKGAVECCPNCRG
HDJ-1	GRNPFDTFFGQRNGEEGMDIDDPFSGFPMGMGGFTNVNFGRS--RSAQEPARKKQDPPVT
HSJ1	SGDPFAELFDDLGP--FSELQNRGSRHSGPFFFTFSSSFPGHSDFSSSSFSPGAGAFRS . . .

76/85

FIGURE 24 (II)

MCG18	TVHDKSAHQTHSSWTPPNAQY---WSQFHSVRPQ-----GP-----QLRQQQHKQN
HDJ-2	TGMQIRIHQIGPGMVQQIQSVCMECQGHGERISPK-DRCKSCNGRKI VREKKILEVHIDK
HDJ-1	HDLRVSL EEIYSGCTKKMK-----ISH-KRLNP---D-----GKSIRNEDKILTIEVKK
HSJ-1	VSTSTTFVQGRRI TTRRIME-----NGQ-ERVEVEED-----GQ-----LKSVTINGVPD . . . *
MCG18	KQVLGYCLLL-----MLAGMGLHYIAFRKVKQMHLNFMDE-KDRIITAFYNEARARAN
HDJ-2	GMKDGQKITFHGEGDQEPGLEPGDIIIVLDQKDHAVFTRRGEDLFMCMDIQLVEALCGFQ
HDJ-1	GWKEGTKITFPKEGDQTSNNIPADIVFVLKDKPHNIFKRDGSDVIYPARISLREALCGCT
HSJ1	DLARGLELSR-RE--QQP-SVTSRSGGTQVQQTPASCPLD-SDLSEDEDLQLAMAYSLSE * . *
MCG18	RGILQQERQRLGQRQPP-PSEPTQGPEIVPRGAGP-----
HDJ-2	KPISTLDNRTIVITSHPGQIVKHGDIKCVLNEGMPIYRRPYEKGRLLIEFFKVNFPENGFL
HDJ-1	VNVPTLDGRTIPVVFK--DVIRPGMRKVPGEGLPLPKTPEKRGDILLIEFEVIFPER--I
HSJ1	MEAAAGKKPAGGREAQHR-RQGRPRPSTKI QAWGGP--RR--VRG--VKQPNVHPQR-RR . *

FIGURE 24 (III)

MCG18	-----
HDJ-2	SPDKLSLLEKLLPERKEVEETDEMDQVELVDFDPNQERRRRHYNGEAYEDDEHHPRGGVQC
HDJ-1	PQTSRTVLEQVLPI
HSJ1	PLAASSSEHRAQPD-----LIQILTGGSDSLWEEKRGVS-----

MCG18	---
HDJ-2	QTS
HDJ-1	---
HSJ1	---

* = amino acid identity in all 4 proteins
- = conservative substitution

78/85

<u>FIG 25 (I)</u>
<u>FIG 25 (II)</u>
<u>FIG 25(III)</u>
<u>FIG 25 (IV)</u>

FIG 25

FIGURE 25 (II)

FIGURE 25 (II)													
AGC	CGC	TTT	GTG	GAG	CTG	AAT	GAG	GCA	TAT	CGA	GTG	CTC	AGT
Ser	Arg	Phe	Val	Glu	Leu	Asn	Glu	Ala	Tyr	Arg	Val	Leu	Ser
			80					85					90
CGT	GAG	GAA	AGT	CGT	CGT	AAC	TAT	GAC	CAC	CAG	CTG	CAT	TCA
Arg	Glu	Glu	Ser	Arg	Arg	Asn	Tyr	Asp	His	Gln	Leu	His	Ser
				95					100				
GCC	AGT	CCT	CCA	AAG	TCT	TCA	GGG	AGC	ACA	GCC	GAG	CCT	AAG
Ala	Ser	Pro	Pro	Lys	Ser	Ser	Gly	Ser	Thr	Ala	Glu	Pro	Lys
105					110					115			
TAT	ACG	CAA	CAG	ACA	CAC	AGC	AGC	TCC	TGG	GAA	CCC	CCC	AAC
Tyr	Thr	Gln	Gln	Thr	His	Ser	Ser	Ser	Trp	Glu	Pro	Pro	Asn
	120					125					130		
GCT	CAA	TAC	TGG	GCC	CAG	TTC	CAC	AGT	GTG	AGG	CCG	CAG	GGG
Ala	Gln	Tyr	Trp	Ala	Gln	Phe	His	Ser	Val	Arg	Pro	Gln	Gly
		135					140					145	
CCG	GAG	TCA	AGG	AAG	CAG	CAG	CGT	AAA	CAC	AAC	CAG	CGG	GTC
Pro	Glu	Ser	Arg	Lys	Gln	Gln	Arg	Lys	His	Asn	Gln	Arg	Val
			150					155					160

81/85

FIGURE 25 (III)

CTG GGG TAC TGC	CTC	CTG	CTC	ATG	GTG	GCA	GGC	ATG	GGC	CTG	551
Leu Gly Tyr Cys	Leu	Leu	Leu	Met	Val	Ala	Gly	Met	Gly	Leu	
	165					170					
CAC TAT GTT GCC TTC	AGG	AGG	AAG	CTG	GAG	CAG	GTG	CAT	CGC	AGC	593
His Tyr Val Ala Phe	Arg	Arg	Lys	Leu	Glu	Gln	Val	His	Arg	Ser	
175	180					185					
TTC ATG GAT GAA AAG	GAC	GAC	CGG	ATC	ATT	ACA	GCC	ATC	TAC	AAT	635
Phe Met Asp Glu Lys	Asp	Asp	Arg	Ile	Ile	Thr	Ala	Ile	Tyr	Asn	
190	195					200					
GAC ACT CGG GCC AGG	GCC	GCC	AGG	GCC	AAC	AGA	GCC	AGG	ATT	CAG	677
Asp Thr Arg Ala Arg	Ala	Ala	Arg	Ala	Asn	Arg	Ala	Arg	Ile	Gln	
205	210					215					
CAG GAG CGC CAC GAG	AGG	AGG	CAG	CAG	CCT	CGG	GCA	GAA	CCC	TCC	719
Gln Glu Arg His Glu	Arg	Arg	Gln	Gln	Pro	Arg	Ala	Glu	Pro	Ser	
220	225					230					

82/85

FIGURE 25 (IV)

CTG CCT CCA GAA AGC TCC AGG ATC ATG CCC CAG GAC ACA AGC	761
Leu Pro Pro Glu Ser Ser Arg Ile Met Pro Gln Asp Thr Ser	
235	240
CCC TGAGAGGGCTT AACTAAATGG GACCTTCATT GGTCCCTCTCC CTGCTGCCCTG	814
Pro *	
245	
TCCAGAACTA CACGTGCAAT AAACCTCATT TCAG (A)n	849

83/85

FIGURE 26

```

human MCG18 MPPLL--PLRLCRLWPRNPPSRLLGAAAGQSRPSTYYELLGVHPGASTEEVKRAFFSK
mouse MCG18 MPSLLQLPLRLCRLWPHSLSIRLLTAATGQRSVPTNYYELLGVHPGASAEIHKRAFFTK
**          *****          *** **.* **** *..*****.***.*****.*
human MCG18 SKELHPDRDPGNPSLHSRFVELSEAYRVL SREQSRSDDDQLRSGSPPKSPRTTVHDKSA
mouse MCG18 SKELHPDRDPGNPALHSRFVELNEAYRVL SREESRRNDHQLHSASPPKSSGSTAEPKYT
*****.*****.*****.*****.*** **.* **** * *****.* * .
human MCG18 HQTHSS-WTPPNAQYWSQFHSVRPQGPQLRQQQHKQNKQVLGYCLLLMLAGMGLHYIAFR
mouse MCG18 QQTHSSWEPPNAQYWAQFHSVRPQGPESRKQQRKHNQRVLGYCLLLMVAGMGLHYVAFR
***** * *****.*****.*****.*..*..*..*****.*****.*****.
human MCG18 KVKQMHLNFMDEKDRITAFYNEARARARANRGIQQERQLGQRQPPPPSEPTQGPE---
mouse MCG18 KLEQVHRFSFMDEKDRITAIYNDTRARARANRARIQQR---HERQQPRAEPSLPPESSR
*..*.* *****.***** *..*****.*****.*****.***.***. **
human MCG18 IVPRGAGP
mouse MCG18 IMPQDTSP
*..*.* *

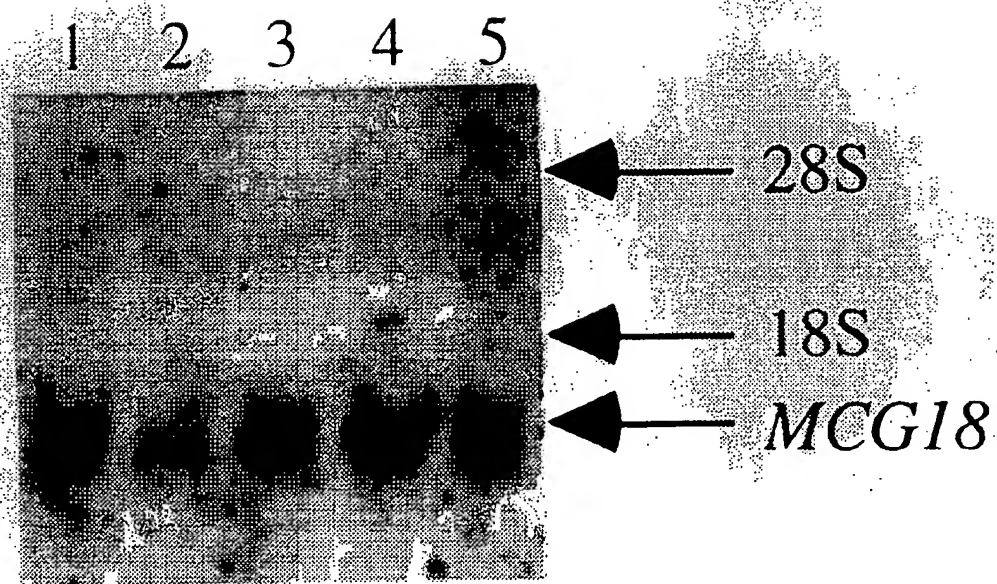
```

84/85

FIGURE 27

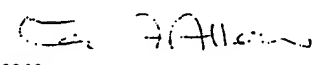
TTGA AGT CTA GCC CCA TCC TGG TCC AAT GCG CTC TTG GTA	40
* Ser Leu Ala Pro Ser Trp Ser Asn Ala Leu Val	
1 5 10	
GCC TCC TTT CCC AGC TGC CCG CCC GCC GCC ATG CCG CCC TTA	82
Ala Ser Phe Pro Ser Cys Pro Pro Ala Ala Met Pro Pro Leu	
15 20 25	
CTG CCC CTG CGC CTG TGC CCG CTG TGG CCC CGC AAC CC	120
Leu Pro Leu Arg Leu Cys Arg Arg Leu Trp Pro Arg Asn Pro	
30 35	

85/85

FIG 28

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 98/00380

A. CLASSIFICATION OF SUBJECT MATTER														
Int Cl ⁶ : C12N 15/12; C07K 14/47; C07K 16/18; G01N 33/53														
According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED														
Minimum documentation searched (classification system followed by classification symbols) I/C: WPAT (D gene) Sequences provided by Applicant														
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched														
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) :EMBL, Genebank, Swiss Prot and PIR: Sequences provided by applicant														
C. DOCUMENTS CONSIDERED TO BE RELEVANT														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
P,X	Kedra D, Seroussi E, Fransson I, Trifunovic J, Clark M, Lagercranz J, Blennow E, Mehlin H, Dumanski J, Human Genetics, October 1997 100(5-6) 611-619 The germinal centre kinase gene and a novel CDC25-like gene are located in the vicinity of the PYGM gene on 11q13 EMBL AC Y12339	1-3,8-10,15-18												
P,X	Guru S C, Agarwal S K, Manickain P, Olufemi S E, et al Genome Research, July 1997 7(7) 725-735. A transcript map for the 2.8-Mb region containing the multiple endocrine neoplasia type I locus TREMBL AC 014616	1, 4-5, 8, 11-12, 15, 19-21												
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/> See patent family annex														
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"E" earlier document but published on or after the international filing date</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means		"P" document published prior to the international filing date but later than the priority date claimed	
* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family													
"O" document referring to an oral disclosure, use, exhibition or other means														
"P" document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search 16 July 1998		Date of mailing of the international search report 20 JUL 1998												
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer GILLIAN ALLEN  Telephone No.: (02) 6283 2266												

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 98/00380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 2, 4, 6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
They are to known groups of proteins and lack distinguishing features which would enable a meaningful search.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Invention 1, defined by claims 2, 3, 9, 10, 16-18, is to nucleotide sequences, amino acid sequences and proteins with a zinc finger domain.

Invention 2, defined by claims 4, 5, 11, 12, 19-21, is to nucleotide sequences and amino acid sequences and proteins which are guanine exchange factors.

Invention 3, defined by claims 6, 7, 13, 14, 22-24, is to nucleotide sequences and amino acid sequences and proteins which are heat shock proteins or heat shock binding proteins.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 98/00380

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EMBL AC AF012106 DT 6 November 1997 Lloyd S E and Thakker R V DE Homo Sapiens DnaJ protein (HSPF ₂) mRNA, complete cds	1,6-8,13-15,22-24
P,X	EMBL AC AF 036875 DT 20 May 1998 Silins G, Grimmond S, Hayward N DE Mus musculus multiple endocrine neoplasia type I candidate protein number 18 mRNA, complete cds	1,6-8,13-15,22-24